REPORT on

"An assessment of the risks of creatine on the consumer and of the veracity of the claims relating to sports performance and the increase of muscle mass"

Referral from: Direction Générale de la Consommation, de la Concurrence et de la Répression des Fraudes (DGCCRF) [Directorate General for Competition, Consumer Affairs and Fraud Prevention]

Report of the Expert Committee on Human Nutrition (Human Nutrition SEC) part of the Direction de l'évaluation des risques nutritionnels et sanitaires (DERNS) [Department of Nutritional and Health Risk Assessment] of the Agence Française de Sécurité Sanitaire des Aliments (AFSSA) [French Food Safety Agency]

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Context of the request

Creatine is a supplement widely used in certain sporting circles for its supposed effects on some performances or on muscle mass, on the basis that it has no risk to health.

The objective of this report is to answer the questions: what are the most common claims? Is it a physiological molecule for the human body? What are its effects on performance and what quantities have to be ingested to achieve them? What adverse effects have been described? Is there a toxicological risk? – in order to be able to state which claims are based on proven scientific fact, at what doses and with what health risks, and to decide what attitude the sports world should have to this product.

1. Introduction: The "creatine phenomenon" in the sports world

Creatine is currently widely used in the sports world and a claim has been made that some 50 % of the sportsmen and women taking part in the Olympic Games were regular consumers of creatine (Williams *et al.*, 1999).

Creatine supplementation is most common in bodybuilders, wrestlers, tennis players, road and cross-country cyclists, rowers, ski jumpers, both Alpine and Nordic skiers, and a many team sports players: rugby, handball, basketball, soccer, football, ice hockey, etc.

A prevalence study has been carried out based on 806 athletes at a major league National College in the United States; 93% replied to the study; 28% acknowledged taking creatine, namely 48% of the men and 4% of the women (LaBotz and Smith, 1999).

1.1 An introduction to creatine

The discovery of creatine and the description of its functions were achieved through the work of biochemists and physiologists; it was discovered in the years 1832-1835 by Chevrel; in 1847, Liebig reported a very high levels of creatine in the meat of wild foxes and later, Heintz and Pettenkoffer described its metabolite, creatinine; in 1912 and 1914, Denis and Faulin reported that the ingestion of creatine was accompanied by a major increase in levels of it in the muscle of cat. Creatine phosphate was discovered in 1927-1929 by Fiske and Subbarow; its level falls during muscle contractions and returns to its initial value during the recovery period.

During high intensity exercise, the hydrolysis of ATP, which is present in small amounts in muscle causing it to be rapidly used up with the need for immediate regeneration, is initially buffered by phosphocreatine through the action of creatine kinase (CK). As phosphocreatine (CrP) is available instantly for the regeneration of ATP, anaerobic glycolysis, with the production of lactate, is induced within a few seconds and the stimulation of mitochondrial oxidative

phosphorylations is again deferred to a greater extent. However, the reserves of phosphocreatine in the muscle are limited, so that during maximum intensity exercise, phosphocreatine is used up in approximately 10 seconds. If it is now possible to increase muscle reserves of phosphocreatine and thus to delay its depletion, this could have a favourable effect on brief and intense exercise.

Creatine has also many other functions in the other energetic systems and in many pathways but it does not seem to be limitating during exercise (see §3.2.6, 4.1 and 6.5).

The use of creatine in sport appears relatively recent, starting in the 1990s, with, however, some anecdotal occurrences presented before then and it has markedly increased since 1995. A number of publications have been devoted to it, of very varied levels; they are usually intended to promote the supposed effects of creatine.

A number of general reviews have also been published, again with very varied methods of presentation (Greenhaff, 1995; Toler, 1997; Mujika and Padia, 1997; Clark 1997 and 1998; Williams and Branch, 1998; Bigard, 1998; Demant and Rhodes, 1999; Juhn and Tarnopolsky, 1999; Feldman, 1999; Juhn, 1999; Jacobs, 1999; Plisk and Kreider, 1999; Silber, 1999; Williams *et al.*, 1999).

2. The claims:

2.1. Greater import has to be given to these claims as they are promoted in media which have a considerable impact. Sheppard *et al.* (2000) observed that popular magazines were the main source of information (69%) on creatine, compared with doctors (14%) and dieticians (10%). They also noted in their survey the frequent use, with creatine, of other anabolic supplements, with known effects on performance, but controversial in terms of long-term health, particularly in young adults: protein, beta-OH-beta-methyl-butyrate, androstenedione or DHEA.

2.2. These are some of the claims drawn from magazines:

"The fourth dimension. Enables overcompensation of strength capacity. Result: 30% more explosive energy." (X-trem Creatine B1®).

"Explosive power. Strength and performance. The essential element of muscle. Increased strength and endurance. Phenomenal increase in performance". (Créatine pure®, société Equilibre Attitude).

"Strength and power" (Société Métrix).

"A natural anabolising formulation enabling a rapid increase in muscle mass. Createk GH3® *contains 5 gr of pure creatine monohydrate per dose with proven anabolising action...* Createk GH3® *provides 4.5 g of L-arginine per dose ... as over 200 studies have shown its effectiveness as a precursor for growth hormone (GH) in increasing muscle mass and reducing fat tissue mass. 5 mg of vanadium sulphate and 100 µg chromium polynicotinate enable the insulinic response to be modulated... Taurine, selenium, branched chain amino acids (BCAA) and glutamine peptide accelerate recovery and control the oxidative damage caused by stress, so training can be resumed more quickly."* (Createk GH3®, MRL).

"Creatine ... permits rapid and effective improvement of muscle mass and tone and sporting performance... Weightlifters and bodybuilders use creatine because it improves protein synthesis in the muscle: twenty studies carried out in the last few years have shown that supplementation with creatine provides an increase in muscle mass ... " (Creatine Surge®, MRL).

"Weightlifters and bodybuilders use creatine because it improves protein synthesis in the muscle· dozens of studies have shown that creatine supplementation provides an increase in muscle mass. Creatine increases endurance, reduces the fatigue associated with training and accelerates recovery. It is especially useful in all sports which demand short and intense "explosive" effort (sprinting, swimming, tennis, football, basketball, etc.). It is no accident that almost all the world's sporting elite has enthusiastically adopted creatine supplementation!" (Creatine monohydrate®).

"The ideal nutritive supplement for anyone involved in sports which require repeated effort or major energy thrusts" (Creatine Source®).

"Creatine promotes increase of the muscle mass, improves endurance, boosts muscle power,

increases energy... Creatine acts by supplying water to the muscle, assisting the production of muscle energy. Prolab® *has recently developed this revolutionary high energy molecule which combines the benefits of pure creatine and pyruvate in a bound molecule. This molecule consists of 60% creatine and 40% pyruvate... an increase in strength and gain in size ... helps to reduce intracellular water retention, reduce body fat and increase lean tissue body mass* (Prolab® creatine pyruvate).

"Undoubtedly the hottest product currently on the sports supplement market is creatine. A wide variety of people from the sports professional to the amateur weightlifter, to the young student athlete... It is estimated that 3 out of 4 athletes who competed in the last Olympic Games were taking creatine... Users of creatine notice an increase in strength levels and in the development of their muscle tissue. This supplement, completely safe, has become the most widely-used in the sports world" (Optimum creatine monohydrate®).

"A natural product which enables you to obtain muscle mass gains comparable to those obtained from anabolic steroids" (Creatine Pro 4®).

"Creatine, a precursor for bio-energy fuel, restores the muscles' ATP levels during maximum contractions" (Weider).

"This nutriment ...is undoubtedly seen today as the most effective natural alternative to anabolic steroids. Why? ...it has been scientifically proved that a large daily intake of creatine, of the order of 10 to 20 g enables, as with steroid products, a major increase in intramuscular cellular volume through a phenomenon known as osmotic overcompensation. Result: protein synthesis is stimulated (anabolism) and the normal natural elimination of the amino acids present in muscle is reduced (anticatabolism). Muscle gain is thus stimulated much more quickly and more efficiently than normal and with absolutely no danger to the creatine user. The second reason... is that the muscle levels of this substance to a large extent determine the duration for which a muscle can be subjected to maximum effort... It is understandable that in order to cope with intensive and repeated training the body should need massive supplementation with this substance if optimisation of physical performance is required. For this reason, when creatine is absorbed your energy and pure strength can be increased in incredible proportions. Some bodybuilders have reported an increase of 20 to 30% in their max in under 2 weeks! ...recover more easily and especially activate muscle repair and building to the maximum " (Mega Creatine fuel®).

"All university studies are unanimous and conclusive: creatine... is genuinely of worthwhile interest for exercise in general and bodybuilding in particular. In effect this substance, produced naturally by the body, and completely free of side effects, enables the bodybuilder ... taken as a supplement to his diet to both:

- spectacularly increase his energy and pure strength...;

- considerably reduce his recovery time between sets and training sessions;

- increase his dry muscle mass in record time unlike any other preparation (especially if creatine is taken along with a diet containing Whey protein!).

So, Muscle Beach® *pure creatine monohydrate, ...should be an essential element of your sports preparation if you want to metamorphose your body in record time and achieve exceptional proportions"* (creatine powder®, Muscle Beach®).

"Gain volume, fast muscle bulking, rapid increase in muscle mass, increased strength and endurance, improved recovery during and after working out" (explosive power 100% créatine pure®, Equilibre Attitude).

"Creatine explosion. Now Optimal Creatine Transport System® tablets *combine more than 5000 mg of pure creatine monohydrate per dose with a special complex of carbohydrates. As you chew the tablets, you release the carbohydrates which have the effect of creating a temporary insulin peak... which will promote the absorption and retention of a higher quantity of creatine and glucose within the muscle. It is precisely this effect of cell volumisation which enables a greater increase in lean tissue mass than that obtained from ordinary creatine.* (Optimal Creatine Transport System®, Genetic Technologies International).

" Pure creatine®. *Strength in its pure state! Saturate your muscles with pure creatine! The new precursor product for energy production (ATP), strength and muscle recovery!* Pure creatine *helps you to increase muscle performance (intensity, strength and duration) and slows the*

formation of lactic acid and ammonia (prevents cramping)". (pure creatine®, Olymp sport).

"Creatine monohydrate with its high-tech transport system and its special nutritive compounds of vanadyl sulphate, taurine, zinc, minerals and vitamins to obtain up to 5 kg additional muscle mass in 4 to 6 weeks" (Creamass®)

"A high-tech product for muscle preparation: sterol/prehormone, pyruvate, HMB, DHEA, androstedion, melatonin... These pre-hormones cause no dangerous side effects, they are found in the most popular supplements in the USA. These are the best products sought after by sports professionals and the most popular as an alternative supplement to steroids." (Nutri search®, the functional food company).

"Advantages· no elements or additives, results scientifically proven, tests show an increase in performance of 5 to 7%. Use is legal, does not contravene sports ethics, not banned by any sports body" (creatine Source®).

It should be noted that these claims featured in magazines published in France in 1999.

In 2000, the claims changed:

"promotes an improvement in muscle strength and power and in faster recovery capacity between training sessions. By enabling intense cellular hydration, a necessary condition for proteinic anabolism, pro pure créatine® *triggers a rapid increase in muscle mass."*

Créastim®*: stimulates the natural production of creatine, the turbo effect.*

"Creatine's effectiveness needs no further proof: taken before a work-out, it enables the release of top level energy and power.".

"But the best creatine is still the one your body produces,... the best... and at the best dosage! For this reason, Creastim® *provides the amino acids L-arginine, L-glycine, L-methionine, essential for the stimulation of endogenous internal creatine production.* Creastim® *also promotes muscular efficiency and optimum recharging of the nerve impulses conduction function and stress management...* (Creastim®, nutrition 21).

"The synergies created by Cell-tech® *with 75g of pharmaceutical quality dextrose, 200 mg of lipoic acid and 10g of creatine generate an optimum anabolic response"* (Cell-tech®, muscle tech).

"Creatine has a multiplicity of effects on the athlete... raising of ATP levels and increase in muscle fibre volume and therefore their contractile power" (chemical pure creatine®, chemical nutrition, Mr.Olympia).

"A cell growth promoter, creatine... provides a considerable increase in muscle volume, thereby contributing to a remarkable gain in strength and muscle weight. More power, more energy in training" (creatine, Tropicana).

"Cell-tech® *is 880% more effective than creatine. During a recent comparative clinical study, the properties of* Cell-tech® *were compared with those of creatine. Athletes supplemented with* cell-tech® *had gained 880% more muscle mass than those who had used creatine monohydrate.* Cell-tech®*'s incredible formula combines 10g pure creatine monohydrate with exactly 75g pharmaceutical quality dextrose and 200 mg alpha-lipoic acid, a substance which potentialises the action of insulin.* Cell-tech® *also contains other key nutrients, acting in synergy to optimise the absorption of creatine by the muscle cells and to induce an impressive increase in volume, strength and power. The athlete using* cell-tech® *experiences astonishing progress. Some achieve a gain of 5 kg mass in only one week! Try* Cell-tech® *and look in the mirror!"* (Cell-tech®, muscle-tech).

"Le pack ultra croissance®,[ultra-growth pack] *a complete first-use kit which stimulate anabolism in a spectacular fashion. Creatine supragen + 2 prometabol + pure and/or protein +... Creatine increases muscle bulk and strength"* (pure explosive creatine®, supragenix).

"Research has shown that creatine supplements enable muscle strength to be increased, tiredness to be delayed, recovery to be facilitated, the production of lactate and ammonia to be reduced and protein synthesis and muscle mass to be increased. Result: strength, explosive muscle power, recovery, fatigue delay, performance" (mega creatine fuel®, Tweenlab).

"As muscle cells can store a not inconsiderable amount of creatine, an additional intake enables the muscles to store up to 50% more" (creatine®, new body).

"Do you want to improve all your performances? A recent study... athletes of a high

standard taking creatine for only 5 days enabled all performances to be improved as well as VO_2max (meaning aerobic capacity). And this applies to all team sports: tennis, cycling, running, football... the capsule formula ... is recommended when seeking performance in aerobic type activities" (creatine, Supragen).

These claims were published in the magazines Flex (Jo Weiders), Jo Weiders Muscle et Fitness, Body Fitness, exercise and nutrition review, and Le Monde du Muscle [World of Muscle].

"No side effects have been recorded when taking creatine."

"For the price of a loaf of bread, the effects of a stick of dynamite. 100 days' loading. Increases muscle mass, fast power boost, increased endurance, improved muscle recovery. Pure creatine, explosive power" (high-tech nutrition, Equilibre Attitude).

"Take the right dose. The muscles are not naturally loaded with enough creatine" (Equilibre Attitude, No. 1 catalogue for sports nutrition).

Several books have been written about creatine (Colgan, 1997; Passwater, 1997; Sahelian and Tuttle, 1998a and b; Burke, 1999). All are North American.

In "Creatine, Nature's Muscle Builder" (Sahelian and Tuttle, 1998): *"sprinters find that creatine boosts their speed, whilst increasing their endurance... Francis Benfato has always been big. Creatine helps him... to shape his muscle mass to perfection... Jo Lazzaro gained 7 pounds of muscle in one year of taking creatine, compared to an annual gain of 1 or 2 pounds he achieved previously... The improvements brought by creatine to Marlin Duncants's physique were much faster and more visible because she is a vegetarian.... The weightlifting coach, Court Elder, says that his lifters benefited from impressive gains in strength and power after only two weeks of creatine supplementation, martial arts practitioners found that creatine boosted the explosive power of their actions, enabling them to achieve faster combinations of punch and kick... Creatine builds strength endurance and self-confidence in people of any age, including the elderly... Cyclists find that the power, speed and endurance which they obtain from creatine enable them to gain precious seconds on their race times... Because creatine provides a long-term fuel source for muscle movement, boxers maintain more combative strength during their matches... Marlin Duncants made enormous progress on definition and vascularity while she was using creatine... The explosive power of swimmers, obtained from creatine, gives them an advantage in competition... Tennis players find that creatine increases their endurance whilst lowering their reaction time."*

"Cell volumisation: for rapid muscle gain... The more the cell fills with water, the more it attracts amino acids. This results in the stimulation of anabolism. This is what researchers call cell volumisation. This volumisation is easy to understand. If the cell fills with water, it is in danger of getting too large and might burst. In order not to burst, it has to strengthen its structure: a powerful anabolising action is triggered... the cell starts to pump amino acids at a faster rate. It is these amino acids which are going to induce durable muscle gain. However, creatine and glutamine don't stop there. Once in the cell these two nutrients will stimulate the anabolism of proteins even more than cell volumisation..."

"Creatine and muscle mass...the authors of this study state that creatine has a direct anabolising effect on the muscles, which explains these gains."

"Creatine and strength. It is not only American doctors of sports medicine who are interested in the effects of creatine. After many years of concentrating on the effects of anabolic steroids on the muscles, the former Soviet researchers have turned to the study of more natural products... in a Performance Research Institute in Lithuania... they used creatine from Ultimate Nutrition®.

"Creatine is safe."

Several websites, mainly North American, sell sports nutrition products by mail order, especially creatine. Not surprisingly, they make very varied claims...

On the other hand, some well-known and well-respected members of sports institutions,

both doctors and scientists, describe creatine to top level athletes as having no effect at all on performance. Others put forward some effects but raise doubts on its safety, in particular when bought from abroad by mail order. Coaches and athletes interviewed told us they were confused and did not understand. The sale of creatine is permitted and is actually freely accessible in several European countries and the USA (but the same applies to melatonin, DHEA, even GH or EPO).

3. Origin and metabolism of creatine

3.1. Status in the body

The body contains approximately 120 g of creatine for an adult male weighing 70 kg; about 95% of the body's creatine (Cr) is stored in the skeletal muscle. About two-thirds is bound with a phosphate in the form of creatine phosphate (CrP), with one third remaining as free creatine. The amount of Cr in the muscles varies according to their type, with white muscle fibres, type 2A or 2B phasic, containing approximately 30% more PCr than the slow red muscles, type 1 tonic, oxidative (Clark *et al.*, 1996b). The content is on average 4 $g.kg^{-1}$ of wet muscle, or 30 $mmol.kg^{-1}$. Expressed in weight of dry muscle, the content is about 4 times higher, the muscle containing approximately ¾ water, or 120 mmol Cr per kg of dry muscle.

It should be noted that this content seems to be well regulated as, even in vegetarians and vegans, who eat little or no animal products, the content is of the order of 120 $mmol.kg^{-1}$ dry muscle (Harris *et al.*, 1992). There is some variation in levels between individuals, with a ceiling, however, even when there is supplementation (see below), not exceeding, on average, 160 $mmol.kg^{-1}$ dry muscle (Williams *et al.*, 1999).

3.2. Metabolism of creatine in the body

3.2.1 Endogenous synthesis. The human body is capable of the endogenous synthesis of Cr, which occurs in the liver, kidneys pancreas... (Walker, 1979). In the human body, this synthesis of Cr is achieved from three amino acids or derivates, two of which are essential, glycine, arginine and methionine. One amidine group is transferred from arginine to glycine to form guanidinoacetic acid. This reaction is followed by the transfer of one methyl group from the S-adenosyl methionine to this acid to form Cr. The synthesis of the Cr seems to be controlled more by the action of amidinotransferase than by that of methyltransferase.

It should be noted that arginine and especially methionine are involved in a number of reactions in the body, but are usually provided in sufficient quantities by the diet.

The endogenous synthesis of Cr is variable, influenced by a number of factors. In particular when there is low availability of Cr in the diet, it is capable of supplementing it, in such a way that the body's content of Cr is maintained with an increase or reduction in the action of the hepatic amidinotransferase.

In people whose diet is balanced and varied and who comply with the advice on dietary reference intake (ANC) in particular for proteins, fats and carbohydrates, endogenous synthesis represents almost half the Cr required daily by the body, the rest being supplied in the diet.

3.2.2. Dietary intake

This varies considerably if a balanced diet is not adhered to, almost nil in vegans; the Cr then comes entirely from endogenous synthesis (Greenhaff, 1997a) and no deficiency or even insufficiency has been described; intramuscular levels of Cr are within the limits of the values described for the rest of the population. In contrast, in individuals who comply with the RDA for proteins, which is approximately $1 g.kg^{-1}.d^{-1}$, 0.5 to 1 g of Cr per day comes from this food. This difference lies in the very varied levels of Cr in food, 4 to 6 $g.kg^{-1}$ for beef, pork or fish (herring, salmon, tuna). Milk, on the other hand only contains 0.1 $g.L^{-1}$ of Cr.

The bioavailability of Cr is very high. Intestinal absorption of ingested Cr is almost total as such, Cr being unaltered by the digestive acid or enzymatic secretions (Harris *et al.*, 1992).

3.2.3. Metabolism in the body

Following its intestinal absorption, the Cr in the plasma is taken up by a number of organs but especially by skeletal muscle; it is found there at high levels. Intracellular transport of Cr is based on two mechanisms enabling its penetration against a concentration gradient, with β2 membrane receptors and the action of an Na-K ATPase:

a) transmembrane transport involves a Na dependent transporter (Clark *et al.*, 1996b), in the membrane sites specific to Cr (Greenhaff, 1997b);

b) the uptake of Cr by the muscle tissue is also influenced by insulin; an increase of it in the plasma, for example following ingestion of glucose, is accompanied by an increase in the uptake of Cr by the muscle.

The transformation of the Cr into phosphocreatine (PCr) or its binding with other intracellular components promotes its retention, as the PCr cannot usually leave the cell (Walker, 1979).

The entry of Cr into the cell is also accompanied by the transfer of water, from which a probable and important osmotic role for Cr.

3.2.4. Breakdown, excretion

In human, PCr is converted above allreversibly in the presence of creatine kinase (CK), into Cr and irreversibly into creatinine in the muscle itself and in proportion to its mass. The creatinine passes into the bloodstream to be excreted in the urine. Approximately 1.7 to 2.5% of the total Cr is excreted each day in the form of urinary creatinine, or in the sweat during major sweat flows, with strong interindividual variability depending on the muscle mass (MM); this is one way of assessing it.

Physical exercise is accompanied by a moderate increase in creatininuria over 24 hours (Kargotich *et al.*, 1997), this, of course, being in the absence of any pathological condition.

During high intensity exercise, repetitive or over a long period, the PCr is converted into Cr and rapidly resynthesised into PCr. It is the same molecules which are re-used a great many times and in this type of exercise, the amount of Cr used during successive dephosphorylations - rephosphorylations would be about 1 kg of Cr. This is therefore a remarkably reversible reaction; in effect, the current estimation of the irreversible breakdown caused during these reactions is very low, about a gram (Williams *et al.*, 1999).

3.2.5. Needs and RDA of creatine

Due to the urinary excretion of creatinine, about 2 $g.d^{-1}$ for a man weighing 70 kg, at a renewal rate of approximately 1.6 $\%.d^{-1}$ of the total CR pool (Balsom *et al.*, 1995 and Williams *et al.*, 1999) and due to the additional protein breakdown in sportsmen, approximately 2 $g.d^{-1}$ are required for the general population and approximately 1 to 2 $g.d^{-1}$ more for the sportsman with major muscle mass and during intensive training.

However, there is no RDA for Cr, as it can be synthesised by the body, based on variable mechanisms which fully satisfy the needs in healthy human.

This particularly applies to the sports population, in particular those involved in strength sports or MM development, who, even more than the general population, benefit from protein intakes which always comply with RDA, even sometimes considerably exceeding them.

3.2.6. Metabolic functions of creatine

3.2.6.1. Energy system. Muscle contractions occur through the sliding of the myofilaments of actin between those of myosin with conversion of the chemical energy originating from the sarcoplasmic ATP into mechanical and heat energy through the ATPasique action of the myosin. ATP, the only molecule used by the myofilaments, is found in low concentrations in the muscle, so only allows a few seconds of exercise. The ATP must be resynthesised immediately from the ADP formed. PCr, 3 to 4 times more concentrated than ATP in muscle, enables, very rapidly and at a high rate, from the start of exercise, this resynthesis of ADP into ATP by supplying a phosphate high in energy when CK is present.

The creatine has to be resynthesised into phosphocreatine. The reaction: PCr + ADP gives

Cr + ATP is reversible. The ATP will be resynthesised by the other energy systems, anaerobic glycosis or, more usually, aerobic, by the oxidation of the glucose and fatty acids.

PCr therefore mainly acts as an energy source with the considerable advantage of its almost instant availability for very high intensity exercise, but, however, only in very short bursts, stores of PCr being quite small; they only cover exercises lasting about ten to fifteenseconds, or rapid changes of power, and are then taken over at a lower intensity by other systems. PCr is very useful for exercise at the very start, if it is very high intensity but its action is very short and transitory. The PCr also acts as an energy-bearing molecule, even a signal, between numerous intracellular sites, though it has not been demonstrated that these activities depend on the cellular concentration of Cr, beyond a reference level, habitually found in the cells and their organelles and environment (Wyss and Kaddurah, 2000).

The accumulation of ADP in the muscle can have an inhibitor effect on muscle contraction as with a certain number of chemical reactions. The PCr then has a buffer action for this ADP which it converts into ATP: $Cr^{2-}P+ADP3^{-} + H^{+}$ gives $ATP^{4-} + Cr$.

3.2.6.2 Acid-base buffer action. Cr also has a buffer action for the H^{+} hydrogen ions in the muscle; during muscular contraction, hydrolysis of the ATP is accompanied, with the activating of the calcium and sodium pumps, by the release of protons which are taken up during the resynthesis of the ATP with the following reaction: H^{+} + ADP + PCr gives, reversibly, ATP + Cr.

During anaerobic lactic exercise, the reduction in the intensity of exercise can be due to the appearance of H^{+} ions, inhibitors of the activity of allosteric enzymes (PFK), which their buffering by the PCr would allow to defer. This seems restricted to high intensity exercise.

3.2.6.3. Osmotic role and effect on protein synthesis. Other functions have been attributed to creatine in healthy human. During its penetration into the cell with the increase in the osmotic pressure, water is then drawn to the cell, leading to intracellular water retention. The hypothesis has been put forward that the Cr could be a signal for the stimulation of protein synthesis due to this increase in intracellular water (Kreider, 1998a and b; Vandenberge *et al.*, 1997a; Ziegunfuss *et al.*, 1997) (see § 5.2.).

3.2.6.4 In pathology. The administration of creatine for therapeutic reasons is currently having interesting effects demonstrated in anomalies in its synthesis, of genetic origin, and in different pathologies.

This is not within the remit of this study.

4. Methods of creatine supplementation

4.1. Theoretical value. While PCr is in concentrations 3 to 5 times higher than ATP in muscle, in fact, in terms of available energy, it is several hundred time less than that originating from the muscle glycogen stores and several thousand times less than that of the triglycerides in the body. So, the energy reserves of Cr are theoretically not very useful compared with those in other substrates. However, all its value lies in its almost instant availability at the start of exercise in relation to the other energy substrates whose availability is delayed, but whose maximum energy release rate is also less.

PCr acts as an energy shuttle between a number of cell sites, which widens its field of interest without it however being demonstrated that this role restricts the reactions involved (see above).

4.2 Commercial creatine. It is almost always in the form of monohydrate, with the claim of greater effectiveness, rather than in the form of citrate. It is presented in powder form, tablets, capsules, syrup, as a drink, chewing gum or sweets. Some **claims mention greater efficiency of the powder form for strength sports and tablets for endurance sports, without any scientific work having provided any justification at all for these alleged differences.**

Creatine is either alone or combined with carbohydrates with the proven justification of

improved intracellular penetration (see below) or with proteins, vitamins, mineral salts, amino acids and sometimes with herb extracts or other phytochemical products.

Though creatine was initially obtained by extraction from beef, Cr supplements are now produced by chemical synthesis in North America, Asia and Europe. (Williams *et al.*, 1999). While creatine can be synthesised almost completely, it is however, usual to use another component of muscle, sarcosine, as the initial material for this synthesis or otherwise cyanamide. Whatever is used, purification of the initial material is required, with the risk of the presence of contaminants with a toxicity (and for what quantities?) which is poorly defined.

While oral ingestion is the most usual, perfusion of Cr is possible, in particular carried out for medical reasons in cardiac surgery as a cardioplegic, for example in Italy with the product Neoton® (Searle Farmaceutici) 0.5, 1 and 5 g, at doses of 5 to 10 g per day. Very few studies seem to have covered the effects of the perfusion of Cr on physical performance or training (Clark, 1996).

Quality controls, carried out to check the purity of the creatine monohydrate, use advanced chemical analysis techniques such as liquid chromatography (HPLC) or high performance capillary electrophoresis, fluorimetry or various methods of humid chemical quantification.

The labelling naturally has to state the ingredients as well as the purity and the checking techniques. And yet, currently no State seems to have put in place a safety and control system for Cr. However, most producers would be obliged to comply with such checks. This means that labelling may be insufficient and the quality of the product should be viewed with caution when the producer is not properly identified, checked by the public authorities and with the opportunity to obtain precise information on quality control by the manufacturer.

Plisk and Kreider (1999) made a request for recommendations on achieving quality control for the sale of Cr supplements: *"the product should be able to be manufactured with the option of an inspection by the United States FDA compatible with current good practice in pharmaceutical production, which covers the whole production line for medicines and special products, from their synthesis to their sale, through all the stages of manufacture, packaging, labelling and sale. Naturally, the product should also comply with the production practices for nutritional supplements. The certificate of analysis should not originate from the distributor or the importer, but from the manufacturer itself, which should be fully identified, with full traceability. Even if it were not compulsory, it would be to the vendor's advantage to provides some information to ensure the product's credibility: its appearance, the analyses conducted using HPLC or HPCE, the density, the size of the grains, the possibilities of pathogenic microbiological contamination, the presence of heavy metals and poisons, the proportion and the content of dry residues and the moisture content and the residues of inorganic materials".* According to Plisk and Kreider, *"respectable producers which adhere to the industry standard would not hesitate to supply this information and the list of their distributors and retailers."*

This aspect is particularly important. The method of cross-border distribution of creatine is sometimes accompanied by the circulation of products whose labelling and provenance are poorly specified.

4.3. Method of supplementation

The creatine content of food being relatively low, ingestion of large quantities of Cr would have to come from an intake of fish or meat increased by several hundred grams, even up to 2 kg during the loading period. It is estimated at 0.3 $g.kg^{-1}$ of body weight, which is about 20 to 30 $g.d^{-1}$ divided into at least 4 equal doses a day, of 5 to 7 g dissolved in about 250 mL of drink, doses taken early in the morning, at lunchtime, in the afternoon and in the evening for a period of from 5 to 7 days.

Next, during a period of weeks or even months, the maintenance dose is 0.03 $g.kg^{-1}.d^{-1}$, or about 2 to 3 $g.d^{-1}$ (Hultman *et al.*, 1996). Up to 5 $g.d^{-1}$ is sometimes advised during the maintenance period: almost all is absorbed and the excess amount ingested, not fixed in the muscle, is excreted in the urine. **It should be noted that over 3 $g.d^{-1}$ or more, this is definitely a supplement, well in excess of needs. With 2 or 3 $g.d^{-1}$, the value of the supplementation is highly disputable, as the excess intake is low. The creatine ingested is added to that in the diet but replaces that synthesised by the human body which is then inhibited. The benefit is then very slight, at least**

for an athlete...

The loading phase can be more gradual, with an intake of 3 $g.d^{-1}$ for one month (Hultman *et al.*, 1996) with similar effects described.

Naturally, to be more precise, the dose should be related to kg of muscle mass.

4.4. Kinetics of the ingested creatine

The intestinal absorption of Cr supplements is total, with no increase in Cr or creatinine in the stools following supplementation (Williams *et al.*, 1999).

The plasmatic peak of Cr appears in the hour following its ingestion and, to maintain a sufficient peak for good intracellular penetration, repetition of the ingestion is recommended in sufficient quantities, 4 to 5 times per day during the loading phase (Harris *et al.*, 1992). It should be noted that Greenhaff (1997a) estimated that over 20 $g.d^{-1}$ after 5 days *"had no additional beneficial effect and moreover was very hard on the wallet!"*

A few hours after the peak, the Cr is cleared from the plasma.

At the start of the loading phase, a reduction in diuresis (- 0,6 $L.d^{-1}$ approximately) is noted for the first 2-3 days, evidence of water retention. This is confirmed by an increase in body weight (see § 5.1.).

Intramuscular content was assessed by biopsy or by nuclear magnetic resonance or by phosphorus 31 spectroscopy (Kreis *et al.*, 1997).

During the loading period, only some of the Cr was retained and on the first day, 25 to 40% was found in the urine and on the third or fifth day, 48.5 to 68%, so half or more (Harris *et al.*, 1992; Maganaris and Maughan, 1998).

Acute supplementation with Cr was accompanied by an almost 90-fold increase in urinary concentration, with clearance increased 26.1 times, which is 60% of the Cr ingested (Poortmans *et al.*, 1997). Moreover, no significant difference was noted in the levels of creatinuria or creatinine clearance during the first days of loading.

With Cr supplementation, endogenous synthesis markedly diminishes (Walker, 1979) but would be completely reversible (Greenhaff, 1995) within 4 weeks following the end of supplementation. This would seem to occur through an inhibition of the action of amidinotransferase, which specifically controls the biosynthesis of Cr, rather than methyltransferase.

The return of the muscle Cr to its initial level, following the end of supplementation, is a very slow phenomenon, in 4 to 5 weeks, with its conversion into creatinine.

4.5. Creatine supplementation, storage and muscle level (Table 1)

Table 1. Variation in the muscle level of creatine during creatine supplementation (from Williams *et al.*, 1999)

Authors	Year	Number	Population	Results
Harris *et al.*	1992	12 5	Men (M) Women (W)	20 % incr * TCr 36 % incr PCr
Greenhaff *et al.*	1993a	10 2	M W	20 % incr PCr 11 % incr PCr
Greenhaff *et al.*	1994a	8	M	15 % incr TCr
Balsom *et al.*	1995	7	M	18 % incr TCr
Febbraio *et al.*	1995	6	M	Incr NP
Lemon	1995	7	M	8 % incr PCr/β-ATP
Casey *et al.*	1996	9	M	15 % incr TCr
Green *et al.*	1996a	21	M: Cr : glucose only Cr + glucose	18 % incr TCr 22 % incr glycogen and 4 % decr TCr 27 % incr TCr 48 % incr glycogen

Hultman *et al.*	1996	31	M	20 % incr TCr
Myburgh *et al.*	1996	13	Trained cyclists	21 % incr TCr
Rossiter *et al.*	1996	19	Rowers	25 % incr TCr approx
Ruden *et al.*	1996	5 4	M W	15 % incr
Thompson *et al.*	1996	10	Female swimmers	NS
Vandenberghe *et al.*	1996a	9	M	4 to 6 % incr PCr
Kurosawa *et al.*	1997	4 1	M W	11to 23 % incr (T/NT) °
Odland *et al.*	1997	9	M	Incr TCr / ATP
Vandenberghe *et al.*	1997a	19	W untrained	6 % incr TCr
Zehnder *et al.*	1998	8 1	M W	21 % incr PCr 9 % incr ATP
Vandenberghe *et al.*	1999	9	M	11 to 16 % incr PCr
Volek *et al.*	1999	19	M	22 % incr TCr

TCr: total muscle creatine CrP: creatine phosphate
* incr: increase ° T/NT: trained / untrained

There are consistent reports of a maintenance or an increase in levels of total Cr, of intramuscular Cr and PCr during supplementation, both acute and chronic. This has been observed much more clearly in men than women, in studies involving between 5 and 31 people.

Increases are extremely variable, in general higher in sedentary and vegetarian patients. The average increase is, depending on the study, from 15 to 23%, with maximum levels of 30% and in one, exceptionally, 52% (see Williams *et al.*, 1999). In $mmol.kg^{-1}$, this represents an average increase of 22 $mmol.kg^{-1}$ of dry muscle going from 18 to 27 $mmol.kg^{-1}$, the level going on average from 120-140 to 160 $mmol.kg^{-1}$ dry muscle (Harris *et al.*, 1992; Greenhaff *et al.*, 1993a et 1994a; Balsom *et al.*, 1995; Febbraio *et al.*, 1995; Gordon *et al.*, 1995; Lemon, 1995; Casey *et al.*, 1996; Green *et al.*, 1996a; Hultman *et al.*, 1996; Myburgh *et al.*, 1996; Rossiter *et al.*, 1996; Ruden *et al.*, 1996; Thompson *et al.*, 1996; Vandenberghe *et al.*, 1996a; Kurosawa *et al.*, 1997; Odland *et al.*, 1997; Vandenberghe *et al.*, 1997a; Zehnder *et al.*, 1998; Vandenberghe *et al.*, 1999; Volek *et al.*, 1999).

By combining the ingestion of Cr with glucose, simple carbohydrate with a very high glucose content and strongly insulinosecretor, or proteins (Steenge *et al.*, 2000), transport of the Cr into the muscle increases significantly (10 %), associated with hyperinsulinaemia (Green *et al.*, 1996 a and b).

Muscle exercise, at the time Cr is ingested, is a factor in the increase of its penetration and intracellular storage (Green *et al.*, 1996 b). However, when exercise and the ingestion of carbohydrates are combined, there is no increased effect on muscle Cr level.

The maximum level of intramuscular Cr achieved is an average of 160 $mmol.kg^{-1}$ dry muscle, therefore apparently bringing into play regulatory mechanisms, with however a small number of subjects who slightly exceeded this level.

Thus, one quarter of subjects respond better and one quarter less well, with maximum levels slightly higher or markedly lower than this value of 160 $mmol.kg^{-1}$.

The average rate of an 18-20% increase is the one to remember; consequently, any claim stating a higher increase does not correspond to facts which have been scientifically demonstrated in a reproducible manner.

It should be carefully noted that it is the subjects with the lowest initial muscle Cr levels who benefit from the most significant increases, in particular when they are vegetarians, which is not very common in sportsmen developing lean tissue mass! We should also repeat the fact that the percentage increase of 52 put forward is based on exceptional cases and can therefore not be presented as normal.

The few studies which also monitored the changes in the muscle level of ATP (Harris *et al.*, 1992; Febbraio *et al.*, 1995; Vandenbarghe *et al.*, 1996a and 1997a; Zehnder *et al.*, 1998) did not show in the first cases any change in the ATP muscle level and in the fourth a slight increase of 9%. In 1999, Volek *et al.* did not observe any increase in ATP athough here again the level of total intramuscular PCr was significantly increased, by 22% on average.

In consequence, any claim concerning an increase in intramuscular ATP has not be scientifically proven to date.

5. Creatine supplementation, physical exercise and body composition

5.1. Weight variation (Table 2). Most of the publications concerning Cr ingestion by sportsmen have described the effects on the weight or the body mass, very rarely on body composition which is more difficult to evaluate, bioelectric impedancemetry or biphotonic absorptiometry being less common than scales. As regards the measurement of skin folds, this does not directly assess lean tissue mass and its reliability is insufficient for measuring small variations in composition.

Table 2. Effects of creatine supplementation on body weight and/or composition (from Williams *et al.*, 1999, and Poortmans and Francaux, 1999, completed)

Authors	Year	Population	N	Δ %
Balsom *et al.*	1993	Men (M) highly trained	18	1.2
Balsom *et al.*	1993	Active M highly trained	16	1.3
Greenhaff *et al.*	1994a	Leisure athletes	8	2
Stroud *et al.*	1994	Physically active	8	1.3
Viru *et al.*	1994	Middle distance runners	10	2.5
Balsom *et al.*	1995	Physically active	7	1.4
Dawson *et al.*	1995	Healthy active M	22	0.9
Earnest *et al*	1995	Weightlifters		1,9
Barnett *et al.*	1996	Active in leisure	17	NS
Green *et al.*	1996a	M	21	1,1
Green *et al.*	1996b	Healthy M	22	2.6
Mujika *et al.*	1996	Swimmers	20	1
Redondo *et al.*	1996	Highly trained athletes	22	NS
Thomson *et al*	1996	Swimmers		NS
Vandenbergh et al	1996	Active M		NS
Becque *et al.*	1997	Weightlifters	23	2.3
Cooke and Barnes	1997	Active M	80	1.2
Godly et Yates	1997	Highly trained cyclists	16	NS
Goldberg and Bechtel	1997	Am football players and athletes	34	0.9
Grindstaff *et al.*	1997	Junior swimmers	18	NS
Hamilton-Ward *et al.*	1997	Athletes	20	NS
Kirksey *et al.*	1997	Athletes	36	2
Prevost *et al.*	1997	Active college students	18	NS
Stout et al	1997	Football players		NS
Terrillion *et al.*	1997	Runners	12	NS
Vandenberghe *et al.*	1997a	Healthy sedentary subjects	19	0 */ 2
Volek *et al.*	1997a	Active healthy M	14	1.8
Bermon *et al.*	1998	Older or in resistance training	32	NS
Ensign *et al.*	1998	U.S. Navy sailors	24	NS
Kelly et Jenkins	1998	Trained weightlifters	18	3.2
Knehans *et al.*	1998	Junior American football players	25	4.4 °
Kreider *et al.*	1998	American football players	25	2.5°°

Larson *et al.*	1998	Football players	14	NS
Maganaris and Maughan	1998	Weightlifters	10	2.2
McNaughton *et al.*	1998	Advanced canoeists	16	2.3
Miszko *et al.*	1998	NCAA IA softball players	14	NS
Noonan *et al.*	1998b	College athletes	39	2.58
Ööpik *et al.*	1998	Karateka	6	1,3
Snow *et al.*	1998	Active people not in training		1.4
Stone *et al.*	1998	American college football players	9	2.5
Thompson *et al.*	1998	Swimmers	10	NS
Ziegenfuss *et al.*	1998a	Omnivores	16	1.8
Ziegenfuss *et al.*	1998b	Runners	10	2.0
Wood *et al.*	1998	People in strength training	44	NS
Francaux and Poortmans	1999	People in resistance training or not	25	2.9
Pearson *et al.*	1999	American college football players	16	1.3
Peeters *et al.*	1999	People in strength training	35	3.5
Rawson et al	1999	Older subjects	20	NS
Stone *et al.*	1999	American college football players	11	3,6
Stout *et al.*	1999	American football players	24	NS
Volek *et al.*	1999	People in resistance training	19	2.0 ** 6.3 **
Becque *et al.*	2000	Volunteers	23	2.3
Deutekom *et al.*	2000	Highly trained rowers	23	1.9
Jakobi *et al.*	2000	Fairly active M	14	1.4
Shomrat *et al.*	2000	Vegetarians vs meat eaters	NP	1.5
Brenner *et al.*	2000	Lacrosse players	16	x
Rawson and Clarkson	2000	Older M	76	0.6
Vogel *et al.*	2000	M	16	1.5 vs 0.8

* stable according to Poortmans, approximately 2% according to Williams *et al*
** after 1 and 4 weeks, in training, in absolute value (not compared with the control group and no deduction made of effects of training and the ingestion of other products)
° Variation in lean tissue mass (by hydrostatic densitometry or bioimpedancemetry)
°° 1% according to Poortmans and Francaux
x reduction of percentage of fat tissue mass (NP), calculated from the measurement of the thickness of skin folds

About one third of the many publications which have dealt with Cr supplementation in the sportsman report no significant variations in weight. The other two-thirds show variations going from 0.8 to 2.9%, at the most, in bodyweight, achieved in the first few days, with no subsequent alteration, while Cr only supplementation is continued.

Some publications, in which the experimental conditions are badly defined, report higher percentages: but the ingestion of Cr is probably accompanied by the taking of other products, some not controlled, and by training which may be intensive. Results should be based on a comparison with work in identical conditions, with the taking of Cr as the only difference.

It was therefore a maximum of 0 to 2.5 kg of bodyweight which was gained. This increase in weight can be an annoying factor for sportsmen in weight categories. It must be systematically stated, as most of the responsible authors do, that sportsmen belonging to these categories (wrestling, judo, boxing, even weightlifting...) must be especially careful with any ingestion of Cr as they will have greater difficulty in controlling their bodyweight.

All except 5 of these studies concern men. In women taking Cr supplements, no significant variation in weight has been reported to date (Poortmans and Francaux, 1999).

The reason for the inter-individual variability in weight gain, effectively limited as it does not exceed 3%, has not yet been clearly explained. It would seem to be broadly connected to daily diet on the one hand and on the other hand to pre-existing Cr status. This clearly emphasises that variation in weight is largely dependent on the increase in intramuscular Cr.

Consequently, any reported increase in bodyweight of over 3% can be considered as not being solely the result of the ingestion of Cr. Claims stating that superior weight gain has been achieved in a few weeks solely as a result of the ingestion of Cr are therefore false. The use of other products is a strong possibility, very common in strength related sports, for which the creatine pretext provides good camouflage, a very convenient alibi.

5.2. Cause of weight variation

5.2.1. This seems to result from *water retention* caused by the osmotic effect produced by the increase in intracellular Cr in the muscle. This could explain why after stopping Cr supplementation, weight increase falls over several weeks, concurrently with Cr levels.

It seems to have been well demonstrated that the weight increase involves mainly lean tissue mass, with a retention of intracellular water especially in the muscle, and not dry mass: proof of this lies in the fall in diuresis of about 0.6 l from the first few days of supplementation (Hultman *et al.*, 1996). Use of bioimpedancemetry enabled the demonstration of an increase in total body water, especially intracellular (Ziegenfuss *et al.*, 1997 and 1998b). It was possible to calculate (Williams *et al.*, 1999) that for 30 to 40 g of Cr retained in the body during the first few days of supplementation, approximately 0.5 to 1 kg of body weight was gained, with about 15 ml of water fixed by per g of Cr retained and the possible role of sodium: cell uptake of the Cr is sodium dependent. This is currently only a hypothesis.

5.2.2. The uptake of amino acids with increased protein synthesis is another hypothesis. While *in vitro* (culture of muscle cells, mononuclear or in differentiation phase, or cardiac tissue from mouse foetuses) stimulation of the synthesis of the two major contractile proteins, myosin and actin, has been demonstrated (Ingwall *et al.*, 1972, 1974 and 1976, Bessman and Mohan, 1992, Flisinska-Bojanowska 1996), in contrast other, more recent work does not confirm these initial observations (Brannon *et al.*, 1997 and Fry and Morales, 1995). Similarly, no publication has yet reported significant effects of Cr on muscle protein synthesis in healthy Man.

According to Poortmans and Francaux, 1999 "from all this work, one cannot conclude a fundamental role for Cr in protein synthesis observed in vivo. There is currently no experimental evidence from human subjects".

The only preliminary evidence reported of an increase in nitrogen status (reduction in breakdown or increase in synthesis), measured using glycine N15 in weightlifters following brief Cr supplementation, was presented by Zigenfuss *et al.* (1997). But in fact it *"transpires that this is speculation and research is needed to confirm it"* (Williams *et al.*, 1999).

Naturally, an increase in dry mass has been proposed in addition to hydric mass, in the majority of cases. Several studies have shown an increase in dry muscle mass with Cr supplementation greater than with the use of other amino acids (Kreider *et al.*, 1998b; Williams *et al.*, 1999; Francaux and Poortmans, 1999). In fact, these are hypotheses and no scientific argument has been made in favour of a change in the muscle protein metabolism and one author recently stated that *"it was advisable that this research be confirmed".*

Consequently, any claim mentioning an increase in the muscle mass implying that of a protein type or an effect on protein synthesis resulting from Cr supplementation, should be considered as having no scientific basis.

In addition, during loss of bodyweight, the ingestion of Cr could be a factor in slowing this weight loss (Ööpik *et al.*, 1998). Thus, karatekas following a hypoenergetic regimen lost 4.3% weight in 5 days and only 3% if under the same regimen they ingested Cr. Moreover, with Cr supplementation, due to the hypoenergetic regimen with a reduction in carbohydrate intake, storage of intramuscular Cr is reduced and as a result, the effect on sports performance (see below) is

greatly reduced.

This increase in bodyweight may therefore have damaging consequences on performances involving the mobilisation of bodyweight with elevation of the centre of gravity, or with strong drag in forward movement as in swimming (hydrodynamic). This could be one explanation for poorer performances during competitive running, swimming or high jump (Balsom *et al.*, 1993b; Mugika *et al.*, 1996; Miszko *et al.*, 1998). But this involves a few studies, others do not report such ergolytic effects resulting from the increase in bodyweight (see below).

6. Creatine supplementation and ergogenic effects

6.1. Methodology. A large number of publications are currently available which describe the effects of acute or chronic supplementation on sporting performance. The difficulty lies in the credibility which can be attached to their results. In effect, a majority of published work appears in documents, journals, magazines, even brochures which do not state the conditions under which results were obtained and the control methods for their publication. And yet, on reading a number of reports, it would appear that one or more criteria acknowledged as essential for a scientific study have not been complied with, with some serious bias. These are the criteria in question, which are fully recognised by scientists (Williams *et al.*, 1999):
"Conditions for a study of creatine supplementation".
Properly controlled studies exploring the effects of creatine supplementation on different types of exercise or sports performance, body mass and composition and state of health, normally comply with the following conditions:
- use of subjects trained for exercise or sport;
- use of validated and reproducible tests;
- use of a placebo control;
- randomised designation of subjects given supplementation;
- use of a double blind protocol;
- control of extrinsic factors;
- use of appropriate statistical techniques".

In the field of epidemiological studies, the data are even more restricted. *"Cr supplementation is widespread, but it is a recent phenomenon and considerable time is still required for possible chronic health problems to develop and for this reason, we currently have very little epidemiological data concerning damaging health effects of chronic Cr supplementation on large populations of individuals".* (Williams *et al.*, 1999).

On this basis, Williams *et al.* (1999) were able to publish a book based on a process of scientific analysis (meta-analysis), of 250 pages, covering 80 publications, 70 research abstracts and 35 journal articles.

This is worth emphasising. **In effect, a great many claims refer to studies which are in fact only pseudo-scientific, as they do not comply with one or several of the required criteria, quoted above and recognised by the whole scientific community. In these conditions, the claim is unjustified.**

6.2. Intramuscular creatine and theoretical ergogenic effects

Maximal anaerobic alactic (AA) capacity (Cmax) is the amount of energy (in Joules) which can be supplied from the AA system, muscle ATP and PCr. In theory, all the exercises, and only these, associated with this should benefit from an increase in the level of muscle Cr proportionally to it. For the other energetic systems, Cr shuttle does not seem to be limiting factor.

With an increase in initial muscle PCr level, in addition to AA Cmax, regeneration of PCr could be faster, thus enabling short and intensive exercises to be repeated more effectively. This should therefore mainly concern high intensity, repeated exercises lasting up to 15 seconds or to a lesser extent, 30 sec., 1 minute at the most, with fewer and fewer significant effects after 10-15 sec.

As a general rule, when one compares the claims with the publications to which they

refer, one can be surprised that hypotheses which appear in these publications are presented as accepted facts. Even negative results, the absence of effect of Cr on certain markers, are sometimes deemed positive for the sole reason that their authors have taken the trouble to measure them. This applies, for example, to plasma levels of lactate and ammonia.

Due to the great many sportsmen taking Cr, the wide variety of the claims and the diversity of the types of physical and sporting activity, the effects of Cr ingestion on the different performances will be detailed based on the type of exercise.

6.3. Exercises based on the anaerobic alactic system, high intensity and lasting less than 30 seconds, single or repeated.

6.3.1. Exercises involving maximal voluntary isometric strength (MVS) (Table 3).

Table 3. Effects of creatine supplementation on brief and intensive exercises, with a duration of less than 30 sec., single or repeated:
Exercises based on isometric strength (from Williams *et al.*, 1999, completed)
M: man; W: women; Ergogenic effect: Y: yes; N: no; Δ%: percentage variation: NS not significant; NP: not provided

Authors	Year	Type of population	N	Ergogenic effect	Δ %
Lemon *et al.*	1995	Physically active	7	Y	11
Vandenberghe *et al.*	1996a	Healthy M	9	N	
Kurosawa *et al.*	1997	Healthy M	5	Y	20
Tarnopolsky *et al.*	1997	Patients intolerant of exercise	7	Y	19
Bermon *et al.*	1998	Elderly people	32	N	NS
Maganaris, Maughan	1998	Healthy M	10	Y	10
Rawson *et al.*	1998	Older M	16	N	NS
Stevenson et Dudley	1998	Resistance trained	19	N	
Urbanski *et al.*	1999	Trained college students	10	Y m inf/N m sup	NP
Jakobi *et al.*	2000	Active men	14	N	NS

These are maximal very short exercises, for which the muscle contractions develop a closed kinetic chain strength in such a way that there is no visible shortening or movement (measure carried out using dynamometer, see Vandewalle *et al.*, 1987).

In the ten or so studies carried out, half show effects of an increase in VMF with Cr supplementation, on average 15%; for the others, the effect is not significant. No reduction effect was observed.

Consequently, claims referring to an improved maintenance of isometric strength during the repetition of exercises of this type seem to be unjustified, with an effect at best of an average of 15%.

6.3.2. Creatine supplementation and isotonic strength (Table 4)

Table 4. Effects of creatine supplementation on brief and intense exercises, with a duration of less than 30 sec., single or repeated:
Exercises based on isotonic strength (from Williams *et al.*, 1999, completed)
M: man; W: women; Ergogenic effect: Y: yes; N: no; Δ%: percentage variation: NS not significant; NP: not provided

Authors	Year	Population	N	Ergogenic effect	Δ %
Earnest *et al.*	1995	Weight trained	8	Y	6

Becque *et al.*	1997	Weightlifters	23	Y	28
Volek *et al.*	1997a	Healthy active men	14	Y	28
Goldberg and Bechtel	1997	Football players and athletes	34	N	
Hamilton-Ward *et al.*	1997	Athletes	20	N	
Crowder *et al.*	1998	American footballers	31	Y	NP
Kelly and Jenkins	1998	Weightlifters	18	Y	7.8
Knehans *et al.*	1998	American footballers	25	Y	4.9 and 8
Kreider *et al.*	1998b	American footballers of a high standard	25	Y	40
Larson *et al.*	1998	Football players	14	Y	NP
Noonan *et al.*	1998b	Young athletes	39	Y	5.8
Pearson *et al.*	1998	American footballers	16	Y Y	3.4 21.5
Warber *et al.*	1998	Soldiers	25	Y	14.4
Bermon *et al.*	1998	Older M and W	32	N	
Stevenson and Dudley	1998	Resistance trained	19	N	
Syrotuik *et al.*	1998	Subjects starting resistance training	21	N	
Wood *et al.*	1998	Weight trained	44	N	
Peeters *et al.*	1999	Strength trained	35	Y	9.6
Stone *et al.*	1999	American footballers	42	Y Y	10.2 8.9
Stout *et al.*	1999	American footballers	24	Y	NP
Volek *et al.*	1999	Resistance trained	19	Y	24 32
Vukovich and Michaelis	1999	M	48	Y	NP
Stout *et al.*	1999	American footballers	24	N	
Brenner et al	2000	Lacrosse players	16	Y	6.2 vs 2.8
Becque *et al.*	2000	Trained M with additional weights	23	Y	28.3 vs 16.1
Syrotuik *et al.*	2000	Resistance trained	21	N	

* Creatine and various supplements (pyruvate...)

A large number of studies concern the effect of Cr on the development of isotonic strength, with single or repeated movements, most often found in weightlifting. Most of the published studies, twenty out of thirty, show an increase or more often a maintenance, while without creatine this reduces, in isotonic strength during repeated movements with varying recovery intervals.

As a result of training, the number of repetitions prior to exhaustion, wrongly called local anaerobic fatigue, is higher with Cr in three-quarters of cases. This has almost always only been observed in men. A single study demonstrates an ergogenic effect in women. Very few studies show no significant ergogenic effect with Cr without it being possible to state the reasons for this.

Consequently, any claim referring to an improved maintenance of isotonic strength during repeated movements as found in weightlifting in men would seem to be acceptable, if it states, however, that the effects are not observed consistently. In women, there are no proven claims.

6.3.3. Isokinetic strength and torque (Table 5)

Table 5. Effects of creatine supplementation on brief and intense exercise, with a duration of less than 30 sec., single or repeated:
Exercises based on isokinetic strength (from Williams *et al.*, 1999, completed)
M: man; W: women; Ergogenic effect: Y: yes; N: no; Δ%: percentage variation: NS not significant; NP: not provided

Author	Year	Population	N	Ergo. effect	Δ %
Greenhaff *et al.*	1993b	Physically active	12	Y	6.8
Brees *et al.*	1994	Vegetarians vs meat eaters	20	N	
Grindstaff *et al.*	1995	Resistance trained	18	Y	6
Almada *et al.*	1995	Resistance trained	18	N	
Vandenberghe *et al.*	1996a	Healthy volunteers	9	Y	23
Kreider *et al.*	1996	Football players	43	N	
Johnson *et al.*	1997	Healthy volunteers	18	Y/N	6/NS
Vandenberghe *et al.*	1997a	Healthy sedentary subjects	19	Y	25
Ziegenfuss *et al.*	1998a	Omnivores	16	Y	7.4
Hamilton-Ward *et al.*	1997	Athletes	20	N	
Kreider *et al.*	1995	Resistance trained	18	N	
Gilliam *et al.*	1998	Active, not trained	23	N	
Rawson *et al.*	1999	Older people	16	N	
Vandenberghe *et al.*	1999	Healthy volunteers	9	Y	5-13
Rossouw *et al.*	2000	Well-trained weightlifters	13	Y	2.6

This is the strength developed against resistance in an appliance which enables excursion of the limb at a constant speed. Of the fifteen studies carried out, about half show an increase with Cr in the isokinetic torque of a mean of 14% with a median of 8%. The positive effect appears to concern mainly the repetition of the movement while the absence of effect seen more in the single exercise. No experiment has shown a detrimental effect of Cr on this type of exercise.

Consequently, claims concerning isokinetic strength should be restricted to stating the inconsistent effects on the maintenance of this strength during repeated movements, in the knowledge that no conclusive work has been carried out on angular speed.

6.3.4. Maximal sprint on ergocycle (Table 6)

Table 6. Effects of creatine supplementation on brief and intense exercises, with a duration of less than 30 sec., single or repeated:
Exercises on ergocycle (from Williams *et al.*, 1999, completed)
M: man; W: women; Ergogenic effect: Y: yes; N: no; Δ%: percentage variation: NS not significant; NP: not provided

Authors	Year	Population	N	Ergo effect	Δ %
Balsom *et al.*	1993a	Active subjects	16	Y	NP
Birch *et al.*	1994	Healthy, fairly well trained	14	Y	10.5
Greenhaff *et al.*	1994b	Healthy leisure athletes	6	Y	4.9
Balsom *et al.*	1995	Physically active	7	Y	5
Dawson *et al.*	1995	Healthy active subjects	22	Y	4.6
Earnest *et al.*	1995	Healthy / strength training	24/8	Y/Y	12.9/18
Cooke *et al.*	1995	Untrained	12	N	
Gonzalez de Suso *et al.*	1995	Trained	19	N	

Casey *et al.*	1996	Healthy	9	Y	4
Barnett *et al.*	1996	Leisure active	17	N	
Burke *et al.*	1996	Swimmers high standard	32	N	
Ruden *et al.*	1996	College students	9	N	
Kirskey *et al.*	1997	Athletes	36	Y	13
Prevost *et al.*	1997	Active college students	18	Y	61
Schneider *et al.*	1997	Untrained	9	Y	6.5
Ziegenfuss *et al.*	1997	Power trained	33	Y	NP
Cooke and Barnes	1997	Healthy active	80	N	
Dawson *et al.*	1995	Healthy active	18	N	
Kirksey et al	1997	M and W college athletes	36	Y	10.8/3.5
Odland *et al.*	1997	Healthy active	9	N	
Jones *et al.*	1998	Hockey players high standard	16	Y	20.7
Kreider *et al.*	1998b	American football players	25	Y	NP
Kreider *et al.*	1998a	Trained / untrained	50	Y	NP
Theodoru *et al.*	1998	Physical education students	20	Y	5.5 and 2.7
Cheltin *et al.*	1998	Resistance trained	33	N	
Snow *et al.*	1998	Active	8	N	
Kamber *et al.*	1999	Well trained students	10	Y	3.5
Vukovich and Michaelis	1999	Resistance trained	48	Y	NP
Ledford and Branch	1999	Trained		N	
Stone *et al.*	1999	American football players	42	N	
Deutekom *et al.*	2000	Well-trained rowers	23	N	
Shomrat *et al.*	2000	Vegetarians / meat eaters	NP	Y	NP
McKenna *et al.*	2000	Healthy volunteers	14	N	
Vogel *et al.*	2000	M	16	N	
Miura *et al.*	2000	M	8	0	13.7/10.9 kJ

This test is very common, being relatively easy to conduct in a laboratory; this explains the large number of publications. Almost 35 studies have been published, the earliest as far back as 1993. From 1993 to 1995, 4/5 ths of the studies are positive; from 1996, only half the studies show a significant increase in the amount of work, or in the power peak, developed during sprints of 10 to 30 seconds. In half the studies, no effect is observed, in particular for the exercises of longest duration, thirty seconds. In fact, at that point, the alactic anaerobic system is replaced by the lactic, which could explain this absence of significant result. The mean increase is 16% and the median 7%.

Consequently, any claim referring to an improved maintenance of quality during short and repeated sprints on an ergocycle in a laboratory, appears to be justified if it states that the effect is significant but is obtained irregularly.

Following the laboratory studies, we present those from the field.

6.3.5. Vertical take-off (Table 7)

Table 7. Effects of creatine supplementation on brief and intense exercise, with a duration of less than 30 sec., single or repeated: Jump exercises (from Williams *et al.*, 1999, completed):
Ergogenic effect: Y: yes; N: no; Δ%: percentage variation: NS not significant; NP: not provided

Authors	Year	Population	N	Ergo. effect	Δ %
Bosco *et al.*	1997	Sprinters and jumpers	14	Y	12
Goldberg and Bechtel	1997	Football players and athletes	34	Y	2.6
Kirskey *et al.*	1997	Athletes	36	N	
Miszko *et al.*	1998	Softball players high	14	N	

		standard			
Noonan *et al.*	1998b	College athletes	39	N	
Stone *et al.*	1999	American football players	42	Y/N	3.5/NS
Stout *et al.*	1999	American football players	24	Y/N	NP/N
Kirksey *et al.*	1999	M and W college athletes	36	Y	7.0 vs 2.3
Mujika *et al.*	2000	High standard football players	17	N	

This is a test carried out in a research centre or in the field, assessing explosive power: vertical jump on the spot with or without prior counter movement. From the ten studies published, it appears that a little over half show a significant increase in vertical take-off, either single or, particularly, repeated, with a mean of 5%. These limited effects are generally attributed to the increase in body weight, which, though moderate, is enough to provide an additional load to reduce the height of a vertical take-off. We note none of the studies includes the application of a corrective coefficient to take into account this weight gain in the vertical take-off height, for the calculation of anaerobic power for example.

Consequently, any claim referring to an improved maintenance of the height of vertical take-off during repeated jumps, seems justified if it states that the benefit is limited and irregular. Any claim to a superior jump height is unjustified.

6.3.6. Sprint, running (Table 8)

Table 8. Effects of creatine supplementation on brief and intense exercises, with a duration of less than 30 sec., single or repeated: Running exercises (from Williams *et al.*, 1999, completed)
Ergogenic effect: Y: yes; N: no; Δ %: percentage variation; NP: not provided

Authors	Year	Population	N	Ergo. effect	Δ %
Redondo *et al.*	1996	Highly trained athletes	22	N	
Goldberg and Bechtel	1997	Am. footballers and athletes	34	Y	
Javierre *et al.*	1997	Sprinters	12	N	
Aaserud *et al.*	1998	Handball players	14	Y	NP
Hutton and Cochrane	1998	Sprinters	7	Y/N	±
Lefavi *et al.*	1998	Baseball players	11	Y	NP
Lefavi *et al.*	1998	Basketball players	37	N	
Noonan *et al.*	1998b	College athletes	39	Y	1.13
Miszko *et al.*	1998	Softball players	14	N	
Smart *et al.*	1998	High standard footballers	11	N	
Thorensen *et al.*	1998	Football players	18	N	
Stout *et al.*	1999	American football players	24	Y	NP
Mujika *et al.*	2000	High standard footballers	17	Y	2
Schedel *et al.*	2000	M	7	Y	1.5
Edwards *et al.*	2000	Fairly active M	21	N	

From the fifteen studies carried out on single or repeated sprints, over 20 to 150 metres, with varying recovery times between each one, it appears that half showed a very small improvement in performance, usually in the form of less deterioration in time between the first and last trial. Finally, Cr supplementation seems rather to improve the recovery period of Cr intracellular levels, with better quality sprint repetitions. This would correspond well to an increase in capacity rather than anaerobic power. In addition, the weight gain, even though moderate, is a handicap which can slightly encumber the sprint of a high standard athlete.

Consequently, any claim referring to an improved maintenance of quality during the repetition of short sprint running races should mention the irregular and limited effect. No

scientific work has shown an effect on the single sprint or on maximal speed.

6.3.7. Swimming (Table 9)

Table 9. Effects of creatine supplementation on brief and intense exercise, with a duration of less than 30 sec., single or repeated:
Swimming exercises (from Williams *et al.*, 1999, completed)
M: man; W: women; Ergogenic effect: Y: yes; N: no; Δ%: percentage variation: NS not significant; NP: not provided

Authors	Year	Population	Number	Ergogenic effect	Δ %
Burke *et al.*	1996	High standard swimmers	32	N	
Leenders *et al.*	1996	High standard swimmers	6	N	
Mujika *et al.*	1996	Swimmers	20	N	
Grindstaff *et al.*	1997	Good junior swimmers	18	N	
Peyrebrune *et al.*	1998	High standard swimmers	14	Y/N	2/NS
Leenders *et al.*	1999	High standard swimmers	32	Y/N	2.5/NS

The swimming performance being in principle 100 metres over fifty seconds or more, the value of ingesting Cr seems less clear, except during training based on repeated sprints of 10 to 50 m. This probably explains the small number of studies found, 6 in total, carried out on swimmers taking Cr supplementation. Only two show significant effects of Cr on performance, envisaged in fact in the form of repetitions of distances of some fifty metres. The other publications show no ergogenic effect from Cr. This is put down to the increase in body weight undoubtedly affecting not density but penetration in the water (hydrodynamics). One can strongly argue as to the validity of this hypothesis, the fact remains that **Cr cannot be considered as having worthwhile effects on swimming performances, whatever they may be (see below also). Therefore to date, no claims have been justified.**

6.3.8. Miscellaneous sports (Table 10)

Ingestion of Cr has been proposed for a number of types of sport in which some of the activity is based on brief, intensive and repeated exercises. In fact, very few studies have been carried out and published which comply with the criteria of scientific rigour.

Table 10. Effects of creatine supplementation on brief and intense exercises, with a duration of less than 30 sec., single or repeated:
Specific exercises for team sports (from Williams *et al.*, 1999)
M: man; W: women; Ergogenic effect: Y: yes; N: no; Δ%: percentage variation: NS not significant; NP: not provided

Authors	Year	Population	Number	Ergogenic effect	Δ %
Goldberg and Bechtel	1997	Am footballers and athletes	34	Y	NP
Jones *et al.*	1998	High standard hockey players	16	Y	3.6
Noonan *et al.*	1998a	Hockey players	12	N	
Lefavi *et al.*	1998	Baseball players	10	N	

For basketball and football players, it is generally sprints and vertical jumps which have been measured: refer to preceding paragraphs.
Ice hockey or baseball players performed tests in the field closer to their actuality, sprints on ice or ball throws. It transpired that 2 times out of 3, the Cr had no effect; there is no significant effect particularly in tests exploring velocity or speed; the positive effects were obtained mainly in the repetition of exercises.

Consequently, any claim concerning a team sport should restrict itself to mentioning a possible improved maintenance of the quality of short and repeated sprints and jumps when repeated, and inconsistently.

6.4. Effects of creatine supplementation on the anaerobic lactic energy supply (high intensity exercises of approximately 30 seconds to 2.5 minutes)

6.4.1. Isometric, isotonic and isokinetic exercises, repeated for 30 sec. to 2.5 min (Table 11).

Table 11. Effects of creatine supplementation on exercises with a duration of between 30 sec. and 2.5 min: Repeated isometric, isotonic or isokinetic exercises (from Williams *et al.*, 1999, completed) M: man; W: women; Ergogenic effect: Y: yes; N: no; Δ%: percentage variation: NS not significant; NP: not provided

Authors	Year	Population	Number	Ergogenic effect	Δ %
Kurosawa *et al.*	1997	Healthy M	5	N	
Maganaris and Maughan	1998	Healthy M	10	Y	20 to 60
Smith *et al.*	1998b	Young vs seniors	9	Y	30
Ööpik *et al.*	1998	Karate	6	N	
Gilliam *et al.*	2000	Active untrained M	23	N	

Here again, it is difficult to come to a conclusion easily, due to the small number and diversity of results. Plenty of meta-analyses are only partial and what is more, faced with the choice of studies and criteria selected, somewhat biased in favour of the ergogenic effects of Cr. Of the 5 studies conducted, selected by Williams *et al.* (1999), 2 show very positive effects and 3 others no effect of Cr supplementation on the exhaustion time at a given percentage of maximal voluntary strength. Among the negative studies, one shows adverse effects, but this was observed in subjects under moderate calorie restriction with weight loss.

Consequently, in the absence of more results, results which are more significant, any claim referring to an improved maintenance of quality during the repetition of exercises of an isometric, isotonic or isokinetic type in a laboratory, over 30 sec. (to 2.5 min) should be considered as not sufficiently justified.

6.4.2. Tests on cycleergometer(Table 12)

Table 12. Effects of creatine supplementation on exercises with a duration of between 30 sec. and 2.5 min.: Pedalling exercises on an ergocycle (from Williams *et al.*, 1999, completed)
M: man; W: women; Ergogenic effect: Y: yes; N: no; Δ%: percentage variation: NS not significant; NP: not provided

Authors	Year	Population	N	Ergogenic effect	Δ %
Febbraio *et al.*	1995	Untrained	6	N	
Jacobs *et al.*	1997	Physically active	26	Y	8.5
Prevost *et al.*	1997	Physically active college students	18	Y	24
Schneider *et al.*	1997	Untrained	9	N	
Nelson *et al.*	1998	Trained athletes	28	Y	13.6
Smith *et al.*	1998a	Active M (untrained)	15	Y	10.8
Vanakoski *et al.*	1998	Trained athletes	7	N	
Stout *et al.*	1999	Junior M	26	Y	9.4 *

* + 30.7°%: 5.5 g creatine + 33 g glucose (9.4% with creatine only)

In 8 studies, maximal exercises lasting 30 (Wingate test) to 150 sec., 5 showed an improved performance on the cycle ergometer by an average of 14%, especially in the untrained subject and the 3 others showed no significant effect. It should be noted that in one study, the "ergogenic" effect of the ingestion of a small quantity of glucose (33 g) was markedly higher than that of creatine.

Demonstration of the value of Cr on performance on cycleergometer in the laboratory for 30 seconds or more has not been achieved, due to the small numbers of significant studies.

6.4.3. Performances in competitive running, swimming and other sports (Table 13 and 14)

Table 13. Effects of creatine supplementation on exercises with a duration of between 30 sec. and 2.5 min.: Competitive running exercises (from Williams *et al.*, 1999, completed)

M: man; W: women; Ergogenic effect: Y: yes; N: no; Δ%: percentage variation: NS not significant; NP: not provided

Authors	Year	Population	Number	Ergogenic effect	Δ %
Viru *et al.*	1994	Middle distance runners	10	Y	1
Bosco *et al.*	1997	Sprinters/jumpers	14	Y	13.2
Earnest *et al.*	1997	M	11	Y	3.2
Terrillion *et al.*	1997	Runners	12	N	
Larson *et al.*	1998	Football players	14	Y	NP
Mujika *et al.*	2000	High standard football players	17	N	

Table 14. Effects of creatine supplementation on exercises of between 30 sec. and 2.5 min.: Exercises in swimming and other sports (from Williams *et al.*, 1999, completed)

M: man; W: women; Ergogenic effect: Y: yes; N: no; Δ%: percentage variation: NS not significant; NP: not provided

Authors	Year	Population	Number	Ergogenic effect	Δ %
Burke *et al.*	1996	High standard swimmers	32	N	
Leenders *et al.*	1996	High standard swimmers	6	Y	3.9
Mujika *et al.*	1996	Swimmers	20	N	
Thompson *et al.*	1996	Swimmers	10	N	
Bosco *et al.*	1997	Sprinters and jumpers	14	N	
Grindstaff *et al.*	1997	Junior high standard swimmers	18	N	
Peyrebrune *et al.*	1998	High standard swimmers	14	N	
Ensign *et al.*	1998	U.S. Navy sailors	24	N	
McNaughton *et al.*	1998	High standard canoeists	16	Y (90 s) Y (150 s)	16.2 13.6
Theodoru *et al.*	2000	Elite swimmers	22	Y/N	1.35/NS

Once again, for tests lasting between 30 sec. and 2.5 min., few studies are available; 6 apparently for competitive running, of which 4 show a positive effect of Cr on performance, both continuous exercise and repeated exercises. In one case, the longitudinal study shows an initial effect which does not increase subsequently. This was reported several times, a significant increase in performance with Cr in the 5 days following the start of acute ingestion, corresponding to the increase in intramuscular levels and without subsequent additional ergogenic effect under the effect of the chronic maintenance dose. According to Williams *et al.* (1999), ***"one can, however, consider that there are some results in favour of an improvement in performance in high intensity competitive running relating to anaerobic glycolysis. These results are still too few and therefore***

***require confirmation"*, before claims are able to mention them.**

Swimming tests, over distances of 100 metres only or of 50 or 100 metres repeated, repeated jumps or courses of obstacles or in canoe, of 90 or 150 sec. were carried out with or without Cr supplementation. Of the ten published studies, it appears that 7 studies show no significant effect from the supplementation. These report a benefit as regards the repetition of middle distance sprints; this is therefore more a condition of training than sports performance.

In conclusion, any claim referring to a beneficial effect from creatine supplementation on sports exercises from 30 sec. to 2.5 min., is not sufficiently justified to date.

6.5. Creatine and aerobic supply (Tables 15 and 16)

Table 15. Effects of creatine supplementation on exercises over 2.5 min.: Pedalling exercises on an cycleergometer (from Williams *et al.*, 1999, completed)
M: man; W: women; Ergogenic effect: Y: yes; N: no; Δ%: percentage variation: NS not significant; NP: not provided

Authors	Year	Population	N	Ergogenic effect	Δ %
Barnett *et al.*	1996	Active, as leisure	17	N	
Myburgh *et al.*	1996	Cyclists	13	N	
Godly and Yates	1997	Well-trained cyclists	16	N	
Engelhard *et al.*	1998	Triathletes	12	Y	18
Smith *et al.*	1998a	Untrained, active	15	Y	7.2
Nelson *et al.*	1998	Trained adults	28	N	
Smith *et al.*	1998a	Untrained active	15	N	
Vanakoski *et al.*	1998	Trained athletes	7	N	
Rico-Sanz and Mendez Marco	2000	High standard cyclists	14	Y	18.1

Table 16. Effects of creatine supplementation on exercises of a duration greater than 2.5 min.: Competitive running exercises and other sports (from Williams *et al.*, 1999, completed)
Ergogenic effect: Y: yes; N: no; Δ %: percentage variation; NP: non provided

Authors	Year	Population	Number	Ergogenic effect	Δ %
Balsom *et al.*	1993	Well-trained men	18	N	
Viru *et al.*	1994	Middle distance runners	10	Y	1.7
Stroud *et al.*	1994	Physically active	8	N	
Bosco *et al.*	1995	Pilots Football players	14 NP	Y Y	NP NP
Rositter *et al.*	1996	Rowers	38	Y	1.1
Thompson *et al.*	1996	Swimmers	10	N	
McNaughton *et al.*	1998	High standard canoeists	16	Y	6.6
Mujika *et al.*	2000	High std football players	17	N	

These are endurance tests: their duration is from 2.5 minutes to several hours.

The effects of Cr on endurance were observed above all during the exercises involving pedalling on the cycleergometer or running. The exhaustion tests lasting one hour, the simulated races over tens of kilometres with or without final sprint, maximal exercises at VO_2max, exhaustion exercise at an absolute or relative exercise power showed, in 4 cases, an ergogenic effect when the endurance exercise was followed by a series of sprints. During exercises lasting 30 min., 40 min or 1 hour with measurement of the distance covered, there was no ergogenic effect observed with Cr

supplementation. Finally, a positive effect was sometimes observed in particular conditions, which do not in fact relate solely to the aerobic supply.

Clearly, while Cr can act as an energy exchange, a shuttle, between the mitochondria and the myofilaments, no restricting effect on this has as yet been demonstrated of the Cr or PCr content in healthy Man.

However, this hypothesis is currently being tested and several propositions have led to very interesting hypotheses with fundamental studies (Roussel *et al.*, 2000; Rico-Sanz, 2000; Rico-Sanz and Marco, 2000; Bessman and Luo, 2000).

It is interesting to note that this brings us in fact into the domain of endurance, in the strictest sense, and only here. In effect, the claim "of improving endurance" very often put forward, in fact almost always concerns the repetition of anaerobic exercises; these are therefore effects on alactic anaerobic capacity or on lactic; so one could accept the concept of anaerobic endurance, but this term could lead to confusion and should therefore be rejected in this sense. This is made more serious by the fact that the majority of sportsmen are involved in team or endurance sports, aerobic endurance, being based largely, in terms of energy, on maximal oxygen uptake (VO2max) and aerobic capacity (maximal aerobic endurance). **To prevent any ambiguity, any claim mentioning any type of beneficial effect of creatine supplementation on endurance should be considered as concerning aerobic endurance and therefore, in terms of scientific work, as unjustified.**

6.6. Creatine supplementation and biochemical indicators of energy metabolism in exercise

6.6.1. Anaerobic alactic exercises

Considered as good indicators of anaerobic glycolysis and the degree of exhaustion during exercise, plasma lactate and plasma ammonia are often measured. We can add that these are also the easiest to measure due to the availability of automatic devices or dry method appliances which appear very easy to use and cost very little. This also means that this facility can lead to abusive use or even interpretation. For this reason, several studies comprising a single, very short and very high intensity exercise lasting a few seconds, present plasma lactates with a rather restrictive interpretation as an insufficient link is made between the possible buffer effect of Cr on muscular acidity on the one hand and the precise interpretation of the plasma lactate, the passage of which from the muscle to the plasma does not necessarily result from simple diffusion...

We have not retained the work referring to pathological states carrying out re-education type exercises.

During brief, single or repeated isotonic exercises, Volek *et al.* (1997a) observed increased or reduced plasma lactate following single or repeated exercises while plasma testosterone and plasma cortisol did not change. According to Greenhaff *et al.* (1993a), plasma ammonia is more likely to be reduced after creatine supplementation during isokinetic exercise.

During brief, high intensity exercises on a cycleergometer, plasma lactate is reduced (Balsom *et al.*, 1995) or unchanged (Birch *et al.*, 1994; Kamber *et al.*, 1999). During more prolonged exercises (Wingate test, 30 seconds), plasma lactate is unchanged (Birch *et al.*, 1994; Earnest *et al.*, 1998; Odland *et al.*, 1997; Snow *et al.*, 1998).

During anaerobic alactic exercise involving anaerobic glycolysis because they last up to 30 sec., plasma lactate undergoes very diverse variations, but the protocols differ greatly and it is not possible to state any general rule at the present time.

Plasma ammonia, in the subject supplemented with creatine compared with one receiving a placebo, is either lower, or not significantly different following isokinetic exercises (Greenhaff *et al.*, 1993a) or on a cycleergometer with markedly an equal distribution between significant effect or absence of effect (Birch *et al.*, 1994; Earnest *et al.*, 1998; Snow *et al.*, 1998).

As regards sprints on foot or swimming, either a tendency towards reduction, or no effect was observed in subjects, whether supplemented or with placebo, on the lactate, ammonia or hyoxantine in the plasma (Miszko *et al.*, 1998; Smart *et al.*, 1998; Thorensen *et al.*, 1998; Burke *et al.*, 1996; Mujika *et al.*, 1996; Peyrebrune *et al.*, 1998). A majority of authors showed no significant

effect on these variables with effects sometimes of increase (Bosco *et al.*, 1995; Volek *et al.*, 1997) or without change or with a reduction in plasma lactate and in only three cases a reduction in plasma ammonia (Andrews *et al.*, 1998; Birch *et al.*, 1994; Greenhaff *et al.*, 1993a, some quoted above).

In conclusion, no claim concerning significant effects on plasma lactate or plasma ammonia from creatine supplementation during short exercises is justified.

6.6.2. Creatine supplementation and biological markers during exercises relating to the anaerobic lactic system (anaerobic glycolysis)

After maximal and repeated exercises of between 10 and 60 seconds, pedalling on an ergocycle, jumps, running, swimming or paddling, plasma lactate was sometimes reduced (Prevost *et al.*, 1997; Burke *et al.*, 1996, as was plasma ammonia: Nelson *et al.*, 1997), sometimes unchanged (Schneider *et al.*, 1997; Vanakoski *et al.*, 1998; Bosco *et al.*, 1997; Terrillion *et al.*, 1997; Mujika *et al.*, 1996; McNaughton *et al.*, 1998; with absence of change in plasma ammonia: Febbraio *et al.* 1995; or a reduction in plasma ammonia: Mujika *et al.*, 1996), or increased again (Earnest *et al*, 1997; McNaughton, 1998 this involving the 150 sec. test as against the previous 90 sec. one).

As Williams *et al.* (1999) concluded, more research is needed in this area to provide reliable conclusions. One of the reasons for these major differences in results, without any trend being involved, relates to exercises with a different basis, either maximal tests in a given time and in which the higher level of plasma lactate could correspond to an increase in the amount of work done and therefore of the lactate produced with a buffer effect of the muscle creatine on metabolic acidosis; or, if it involves a distance to be covered, the total time is a little shorter and some of the energy may come fom the breakdown of phosphocreatine, thus reducing the production of lactic acid.

These different mechanisms are based on hypotheses which would be worth further examination, which reductive claims leave to one side due to an objective which is more result-oriented than scientific.

In conclusion, there is no scientific work providing evidence or conclusions which could justify a claim as to the beneficial and unequivocal effect of creatine supplementation on plasma lactate or plasma ammonia.

6.6.3. Creatine, plasma markers and aerobic system

After exercises lasting a few minutes to multiples of ten minutes, on an ergocycle, running on a track or performances in a canoe, with creatine supplementation compared with a placebo, plasma lactate is either increased (Balsom *et al.*, 1993), or unchanged, which is most common (Barnett *et al.*, 1996; Engelhardt *et al.*, 1998; Vanakoski *et al.*, 1998; Stroud *et al.*, 1994), or reduced (Nelson *et al.*, 1998; but here with possible bias, as randomisation was not observed).

As regards plasma ammonia, hypoxantine and plasma urea, supplementation had no effect (Myburgh *et al.*, 1996) or reduced it, with the bias reported above (Nelson *et al.*, 1998).

Clearly, in the end no claim can be advanced as to a beneficial effect from creatine supplementation on plasma lactate or plasma ammonia and the other associated markers during exercise of any kind, in a healthy subject.

6.7. Creatine and fatigue

One of the main advantages of creatine supplementation lies in the increase in its levels in the muscle, with the effect of increasing anaerobic alactic capacity. This permits work at a given, very high, intensity, for a little longer (a few seconds at the most) and delay of the anaerobic alactic exhaustion point. It must, however, be emphasised that these are very short term exercises, 15 sec. maximum. After about fifteen seconds, the anaerobic lactic system takes over with the availability of a muscle glycogen level which in terms of energy is some 300 times greater than that of phosphocreatine (see above). We therefore feel it is **erroneous to speak of "pushing back fatigue"** by ingesting creatine through the increase, even by 20%, of its intramuscular levels.

In fact, this is local muscle "fatigue", due to the exhaustion point during very brief, repeated and intense **alactic anaerobic exercises**, such as sprints, weightlifting or repeated throws. **The claims as to maximal anaerobic alactic capacity are the only ones which could be justified (see § 6.3.). The term local "fatigue" is being abused; its use in this context could be considered as seeking to mislead the consumer.**

In addition, the rate of anaerobic glycolysis is regulated in particular by allosteric enzymes, such as phosphofructokinase; one of the inhibitors of the process is the level of PCr. When this falls, anaerobic glycolysis gradually starts. Consequently, an increase in intramuscular PCr provides "protection" from the premature onset of anaerobic glycolysis. But the muscle phosphocreatine level in spite of the 20%, at the most, increase due to supplementation, can only be a limited factor compared with the glycogen level; and significant effects are not easy to demonstrate, due to the normal variation of the experimental biological effects observed.

In terms of anaerobic lactic capacity or aerobic capacity, local effects of creatine on the muscle have not been significantly demonstrated.

And no scientific publication to date has covered the effects of creatine on perceived central fatigue which is defined as: *"a painful feeling caused by effort, excessive physical or intellectual expenditure".*

In conclusion, the many claims mentioning beneficial effects on fatigue are not justified.

6.8. Creatine, physical activity and senior athletes

We found 4 studies from 3 different laboratories which had monitored the effects of creatine supplementation in older people undergoing physical training with an emphasis on strength development.

Exhaustion time during a leg extension exercise using the thigh, repeated to exhaustion, was increased with the ingestion of creatine with a clear increase in intramuscular levels of creatine verified by nuclear magnetic resonance. These preliminary results obtained from 5 young and 4 middle-aged (58 years old) people, with 2 or 3 men and 2 women only per category (Smith *et al.*, 1998), remain to be confirmed.

Creatine supplementation or a placebo in 32 people aged between 67 and 80 years showed after 8 weeks of strength training and the taking of treatments, no effect on maximal dynamic strength or on "endurance (or capacity)" in dynamic and isometric strength (Bermon *et al.*, 1998).

Acute creatine supplementation in 17 men from 60 to 78 years of age, showed a small, not significant increase in isokinetic strength with creatine (Rawson and Clarkson, 2000). Acute then chronic creatine supplementation, for 30 days, showed no significant effect on body composition or arm flexor strength but only slightly significantly on anaerobic capacity determined by isokinetic dynamometry (Rawson *et al.*, 1999).

In view of these few scientific results, mostly not significant, no claim is justified on the valuable effect of creatine in senior athletes and older people.

7. Creatine supplementation, health effects and safety of use

This area has been explored only relatively recently because the systematic ingestion of creatine by sportsmen began in the 1990s and more specifically in large quantities in 1995.

In addition, it must be emphasised that the approach here is very different from that for the use of creatine as a medicine: this consists in comparing its beneficial effects on different pathologies in relation to any possible secondary effects on different health indicators, both being carefully weighed up. In terms of the medical indicators for creatine, this involves either short treatments (cardiac surgery, etc.) in major pathologies, in which the benefits/risks ratio is high, or long term treatments for people suffering from an enzymatic deficit of creatine synthesis, with replacement to achieve normal levels and no more. This scenario is one of complementation and not

supplementation.

As regards the ingestion by the healthy male sportsman, possible side effects are not acceptable, one of the main objectives of physical and sporting activity being improved health and increased pleasure.

Clearly, creatine marketed illicitly, to a greater or lesser extent, cannot come within the remit of this document. Products which contain creatine of animal origin should probably be monitored specifically. Equally, some uncontrolled products might contain toxic substances, some associated with the method of extraction.

According to Benzi (2000), a major point should be considered, that of the quality of the production of the creatine with the quantity of contaminants present. During its synthesis from sarcosine and cyanamide, varying levels of contaminants (dicyanamide, dihydrotriasine, etc.) are formed and the tolerable concentrations (ppm) should be defined by appropriate toxicological research.

7.1. Muscle cramps. These have been described several times as a side effect of creatine. This is the most frequently reported side effect, in particular when there is dehydration in a hot atmosphere. The increased uptake of water by the muscle, caused by the increase in creatine, has been mentioned, but this factor does not seem relevant if the sportsman rehydrates as he should (Strauss, 1998; Clark, 1997). Few epidemiological studies (Kreider *et al.*, 1998; Juhn *et al.*, 1999) have stated the frequency of muscle cramps in the sportsman taking creatine. It is often repeated (claim) that this incidence is anecdotal...

7.2. Other muscle, hepatic and cardiac side effects

An increase in levels in the plasma of enzymes from the muscle or the liver have been observed following intense exercise with creatine, more than with a placebo.

Most studies show that in fact, creatine supplementation has no effect on creatine kinase (CK), lactate deshydrogenase (LDH), aspartate and alanine aminotransferase (ALAT and ASAT) or gamma-glutamyl transaminase (g-GT) (Almada *et al.*, 1996; Kurosawa *et al.*, 1997 and 1998b; Engelhart *et al.*, 1998; Mihic *et al.*, 1998; Ransom *et al.*, 1999). However, a few authors have described increases in CK levels in the plasma with creatine during intensive exercise, but these increases seem transitory and could be put down to increased training with creatine, according to observers (Almada *et al.*, 1996; Kreider *et al.*, 1998b). Comparison with subjects using a placebo shows comparable increases in plasma levels of CK, LDH, ASAT or ALAT (Ransom *et al.*, 1999). A type of counter demonstration consisted in observing the plasma levels of these enzymes with the ingestion of creatine but without exercise or with low intensity exercise (Engelhart *et al.*, 1998; Kurosawa *et al.*, 1998b; Mihic *et al.*, 1998). No difference was shown.

Hepatic problems have been mentioned; they have not been confirmed, in particular from the study of plasma levels of total protein, creatinine, urea, bilirubin and enzymes of hepatic cytolysis (Earnest *et al.*, 1996).

In terms of cardio-vascular function, an increase in systolic (SAP) and diastolic (DAP) arterial pressure has been observed, inconsistently. No significant effect has been observed (Mihic *et al.*, 1998; Peeters *et al.*, 1998). And yet creatine is mainly consumed by strength sportsmen: their "resistance" training is a factor in the increase of peripheral resistance with demonstrated increase in SAP and especially DAP. This is what has been able to be observed with creatine. A recent study (Derman, comm. pers., 2000) on 10 subjects taking creatine (Cr) and 10 others taking a placebo (Pl) showed after several months of mixed training (strength and aerobic) a slight increase in average SAP and DAP with the product and no change with the placebo. In fact in the Cr group, only 2 subjects saw their SAP rise significantly, while for 2 others, the high initial values were maintained. Derman concludes an individual susceptibility and the requirement for regular blood pressure monitoring, with immediate cessation of ingestion at any rise in SAP or DAP, as with any other side effect observed with the ingestion of creatine.

In conclusion, creatine supplementation seems to be a trigger factor for pathologies in predisposed subjects, which preventive measures should detect.

7.3. Creatine and renal function

The accusations made with regard to creatine as to its possible adverse effects on health mainly concern renal function. An alarmist article was published in The Lancet (Pritchard and Kalra, 1998) describing the aggravation of serious renal dysfunction when taking creatine and reporting the death of wrestlers on creatine. The case presented therefore concerned a patient already presenting a renal pathology. When creatine supplementation was stopped, the problems receded. What is more, an in-depth inquiry enabled attribution of the deaths to extreme dehydration, while only one of the subjects may have taken creatine. Updates were then published (Greenhaff, 1998; Poortmans and Francaux, 1998).

Extensive research into renal function has been carried out following ingestion of creatine, acute (5 days), medium term (2 months) or very long term (up to 5 years). No adverse effect has been observed on the renal functions studied, clearance of creatinine, urea and measurement of micro-albuminuria, which show no change in glomerular filtration rates and tubular re-absorption (Poortmans *et al.*, 1997, 1998, 1999a and b). Poortmans and Francaux (1999b) also report that about 60% of the creatine load is excreted daily in the urine; this means that exogenous creatine supplementation is often excessive in terms of its take up by the muscle tissue.

These authors say "we feel that prior to any supplementation, an anamnesis must be conducted of the athletes supposedly in good health, in order to detect any renal problem, however minor. It is enough to measure the glomerular filtration rate (clearance of creatinine) and the urinary excretion of plasma albumin... these tests should, in our view, be repeated regularly (every 3 months) during the supplementation period. Any pathological problem must imperatively result in cessation of the supplementation".

Finally, the most notable fact with creatine supplementation is the considerable increase, up to about 90%, of urinary creatine.

This makes the taking of creatine easy to detect.

And finally, renal excretion is strongly stimulated. What are the very long term effects, when other supplements are also ingested, which are known to stimulate hepatic and renal function strongly?

According to Williams *et al.* (1999), fairly favourable in their book to the presentation of the benefits of creatine, but with solid scientific argument, *"it should be noted, however, that few studies have made an in-depth assessment of the effects of creatine on renal function. Consequently, other research using more precise methods to access renal functions is desirable before definitive conclusions can be drawn".* We would repeat that monitoring for longer than 5 years would be desirable, in sportsmen often ingesting more of this than recommended and who might benefit from more organised medical supervision (bodybuilders) to meet the objectives of "health protection".

7.4. Creatine and biological variables

The effects on water retention in the muscle of creatine ingestion have led several authors to carry out biological plasma monitoring. Whether this involves blood haematocrit or haemoglobin, or sodium, chlorine, potassium calcium, phosphorus or the plasma or blood volume, no long-term effects have been observed (Harris *et al.*, 1992; Kreider *et al.*, 1998c; Ööpic *et al.*, 1998, Rasmussen *et al.*, 1999).

In terms of the lipid parameters, creatine supplementation can have a beneficial effect on the plasma profile, with a reduction in total cholesterol and LDL and increase in HDL, over a season and in sportsmen of a high standard (Kreider *et al.*, 1998b; Melton *et al.*, 1999). But one study (Lawson *et al.*, 1998) reported no effect of creatine supplementation on the serum lipid profile.

It is possible to conclude that other research is needed to confirm these preliminary results. Currently, no claim of a proven beneficial or deleterious effect on lipid profile has any scientific basis.

We should indicate that Poortmans and Francaux (1999), Williams *et al.* (1999) and other authors of general reviews reporting possible side effects, indicate the absence of

toxicological data on the other organs, sites of the active metabolism of creatine; in addition to the kidneys, the liver and pancreas, there are also the brain, the heart, the sexual organs....

Clearly, research will be necessary to verify effects on these organs, in particular when large quantities of creatine are being ingested for prolonged periods, sometimes recommended and monitored. An increase, even moderate, in intracellular levels of creatine changes the cell's energy state, which must have repercussions.

7.5. Epidemiological data

Alongside these clinical, biological or experimental observations of the possible toxicological effects of creatine, it is possible to refer to the epidemiological databases. While there is a system for pharmacological surveillance in France, it would seem that we do not have a comparable system for the monitoring of any adverse side effects associated with the ingestion of dietary products.

7.5.1. The Office of Special Nutritionals, Center for Food Safety and Applied Nutrition, of the United States Food and Drug Administration, has set up a website: http://vm.cfsan.fda.gov/~dms/aems.html. giving access to the *"Special nutritionals adverse event monitoring system Web report »*.

A search of this database enables the observation that 2621 adverse effects have been declared relating to 3451 products. For creatine, 32 reports have been made. 26 of these reports concern subjects who have only ingested creatine. The name of the product and that of the company are indicated, they are vary diverse. The adverse side effects reported are very varied, quoted in the order they were recorded: dyspnoea, fatigue, "serious pain", diarrhoea, vomiting, polymyositis, aggressive and violent behaviour, stomach cramps, myopathy, venous thrombosis, atrial fibrillation, one death, stomach burns, migraines, facial rash, cardiac arrest with apoplexy and ventricular fibrillation, repeated epistaxis, thoracic, gastric and backbone pain, intracerebral haemorrhage and rabdomyolysis. The most frequent side effects are digestive.

It should be noted that this list has been very differently interpreted in scientific circles; at best *"it could act as a basis for more in-depth study, with a recommendation of caution whilst waiting for more information"*, at worst, treated with derision, seen as a list of anecdotes.

Account must also be taken of the opinion at the top of this list: *"what should you remember when you use this information system? Reporting is voluntary and the information is reported by the consumer or the health professional. This means that only adverse effects reported to the FDA are found in the database. If an adverse side effect occurs and is not reported to the FDA, it will not appear in the database. The absence of information does not necessarily mean that a product or ingredient is not involved or that it probably has no adverse side effects.*

It is not certain that a reported adverse side effect can be attributed to a particular product or ingredient. The information available may not be complete enough to lead to this certainty.

The total number of adverse effects cannot be used to estimate the rate of incidence in the population. Not all adverse effects are reported and there are no reliable data on the populations using it.

A report of an adverse effect can be affected by a number of factors including the duration or the time at which the product or ingredient were placed on the market or publicised.

Comparison of one product's safety in relation to another cannot be obtained directly from these data. The information available may be insufficiently complete to enable this comparison.

The inclusion of a product as a special nutritional product in this database does NOT necessarily represent its legal or regulatory status. The information available is not complete enough to enable this determination."

In view of the wide variety of cases reported but in very small numbers, the question remains whether these are anecdotal cases or not. The fact remains that this database exists and that it presents a certain number of cases which could be compared with what has been described elsewhere in the literature and which concurs with it.

7.5.2. A bibliographical search with the key words "creatine" and "side effects" and/or creatine and "adverse effects" on *Medline®* (*Pubmed®*, *National Library of Medicine* in the USA) was carried

out by Juhn and Tarnopolsky (1998). It should be noted that this is a strategy similar to that adopted by the European Commission Scientific Committee on Food, with a research on *Medline*®, using the key words "creatine" and "safety".
One could dispute the value of this approach in either case: this database mainly compiles scientific articles published in journals at international level, even though adverse side effects caused by creatine relate more to the description of isolated cases in sportsmen, than to the physiological description of mechanisms.

Juhn and Tarnopolsky (1998) emphasised the paucity of rigorous studies assessing the side effects of creatine supplementation. Finally, they concluded, as regards *"the adverse effects on the cardiovascular system, that long-term studies in man were required; in terms of gastro-intestinal side effects, that diarrhoea and gastro-intestinal pain were found more frequently with capsules of creatine, as opposed to creatine in the dissolved form, but that this had not been studied directly; in terms of the hepatic system, that long-term studies on a young and active population are required; in terms of the musculo-skeletal system that studies with a larger number of subjects are required but no direct evidence of a causal relationship between the use of creatine and muscular dysfunction had been demonstrated; in terms of the neurological system that clearly the effects of oral creatine supplementation on the human brain should be studied further".*

7.5.3. What do the epidemiological studies show?

In a study carried out on a population of 52 baseball and American football players, Juhn *et al,* (1999) reported 16 cases of diarrhoea, 13 of muscle cramps...; 14 subjects showed no adverse effects, 40 subjects were prepared to take creatine again or continue with it. Excessive ingestion of creatine in a single dose or on a daily basis was blamed for most of the side effects or problems presented..., without this hypothesis being properly verified. *"This raises the problem of the monitoring of prescription by a number of dieticians and other nutritionists in the United States, with the need for these professionals to be more involved in the decision-making process in the monitoring of the athlete's nutrition."* (Juhn and Tarnopolsky, 1999).

7.6. Creatine supplementation and mutagenic effects

In terms of possible oncological effects, the phosphocreatine – creatine kinase system could be involved in the processes of cellular oncogenesis. In precise terms, rats supplemented with creatine show an increased growth of Erlisch tumour cells in the ascites (Ohira and Inoue, 1995). However, it has also been shown that creatine inhibits the growth rate of mammary tumours in rats (Miller *et al.,* 1993). But analogues of creatine, which have the opposite effect to those of Cr, reduce the formation of colonies of explanted human tumour cells (Martin *et al.,* 1994). *"Some long-term studies could help to determine if oral creatine supplementation is beneficial, harmful or has no effect on healthy subjects in terms of cellular oncogenesis".* (Juhn and Tarnopolsky, 1998).

In an exhaustive article on the metabolism of creatine and creatinine (Wyss and Kaddurah-Daouk, 2000), with some 105 pages and 1163 references, published in Physiological Reviews, an extremely complete overview is also presented of all the effects of creatine and its analogues on different metabolisms, from a pharmacological standpoint. Insofar as at least two publications, on sport and creatine, have alluded to relationships between creatine and oncogenesis (Juhn and Tarnopolsky, 1998; Rossi *et al.,* 1998), we considered it important to verify if there was more evidence, as these two articles reported other work.

Some experimental arguments seem to demonstrate *in vitro* and also *in vivo* that the action of uncontrolled mitosis seems to occur in some cases of high levels of intracellular creatine and creatine kinase (CK) and therefore of an abnormally high local energy level. The CK system is involved in tumour growth through the regulation of ATP production or its modulation; these are processes which are fairly well-known, but the fact remains that molecules which interfere with this system may have an impact on tumour growth or development. A number of analogues of creatine and phosphocreatine, at least fifty, have now been studied. In particular, cyclocreatine (cCr) reduces the rate of ATP production through CK. This was shown in a large number of tumours characterised by the expression of high levels of CK (Bergnes *et al.,* 1996). The

anti-tumoral action of cyclocreatine has been widely studied. *In vitro*, a correlation has been demonstrated between the CK activity of a tumour and its response to cyclocreatine (Lillie *et al.*, 1993)... In conclusion (Wyss and Kaddurah-Daouk, 2000), *"CK with its substrates creatine and phosphocreatine seems to be associated with the growth of a number of solid tumours and perhaps with metastasis cascade. Further studies are needed to clarify the mechanism of action of the analogues of creatine as anti-tumour agents."*

Clearly, extrapolations are always risky – and we have criticised them enough not to risk abusing them here - and this does not mean that a protumoral effect of Cr and CK observed in certain conditions could be expressed in healthy Man, any more than an anti-tumour effect of analogues of creatine, having the effect of reducing intracellular Cr and PCr, permits the extrapolation of a protumoral effect of creatine when it is used in pharmacological doses in the long-term. However, one must raise the issue of the risk posed to their energy balance by the marked and prolonged increase in creatine in certain cells. And one must also apprehend the risks of poorly-controlled levels of energy activity, especially when very high, in the presence of oxygenated free radicals to DNA, RNA, the membranes... during intensive and repeated exercise.

The other worrying fact is this effect of creatine and β-guanidinopropionic acid on the growth of Erlisch tumour cells in ascites when the concentration of creatine is altered locally (quoted above).

In the same article (Wyss and Kaddurah-Daouk, 2000), **creatine and creatinine** are presented as **probable precursors for mutagens and carcinogens in the category of amino-imidaso-asaarenes (AIA) in cooked food,** especially fried and **grilled**. This mutagenic effect of the AIA compounds formed during the processing of meat products relies on a large number of factors but is well-established, with an effect of increased risk during deep frying or grilling and minimisation during microwave cooking (Ref. 119, 743, 807, 902, 903, 919 and 1009 in Wyss and Kaddurah-Daouk, 2000.). Wyss and Kaddurah-Daouk present 5 groups of arguments to demonstrate that creatine or creatinine are important precursors of AIA mutagens, referring to validated articles (see Ref. 534, 807, 902, 934, 423, 481, 744, 1066, 721, 904, 236 in Wyss and Kaddurah-Daouk, 2000). But, of course, the basic issue lies in the question: **can what is observed at high temperature be produced at body temperature?** The **incubation** for different periods, of creatine or creatinine, at temperatures from **37** to 250°C in dry or aqueous solution has been carried out, with different compounds and practically all the AIA food mutagens can be produced in these models (Ref. 119, 236, 417, 424, 434, 492, 544, 710, 902 in Wyss and Kaddurah-Daouk, 2000). In a similar fashion to the situation for cooked food, a variety of factors influences mutagen production in different models, with the effects of temperature, incubation time, concentration of antioxidants as well as the type, concentration and proportion of precursors (see Ref. 417, 424, 434, 465 and 902 in Wyss and Kaddurah, 2000).

But above all, **maximal production of mutagens** is obtained **by mixing creatine or creatinine with an amino acid and a sugar** in a molar ratio of 1:1:0.5. Remarkably, almost the same levels between these compounds is found in the muscle (Laser Reuterwärd, 1987). Fructose is more effective than glucose which is more effective than saccharose in this mutagenic effect of creatine or creatinine. Raised levels of carbohydrates, on the other hand, have an inhibitory effect. Of course, one can refer to the Maillard reaction and the Streiker breakdowns to explain these effects, to differences in temperature and incubation periods. While it is true that these reactions are obtained at high temperatures, as regards the formation of certain bodies, a temperature of 60°C (even 37°C) seems to suffice at a pH of 7.4 in an aqueous solution in the presence of sugar or aldehyde (Manabe *et al.*, 1992).

Naturally, we are within the context of pathology when it is written that that patients with chronic renal dysfunction are exposed to an increased risk of cancer. As soon as the increase in creatinine, and possibly of creatine, in the plasma is high, this creates, according to these authors, favourable conditions for the formation of AIA bodies. These have been detected in the dialysate of all patients with uraemia (Yanagisawa *et al.*, 1986). It should be noted that these mutagenic products do not originate from meat consumption (over-grilled, even carbonised) but from *de novo* synthesis (already demonstrated at 37°C, see Manabe *et al.*, 1992).

We should state that AIA are not mutagenic as such but have to be activated by a series of enzymes

which will permit them to exercise their mutagenic effect. The presence of oxygenated free radicals and the intervention of the P450 cytochrome enzymes have an important role in this promutagenic transformation (Hammons *et al.*, 1997; Anari *et al.*, 1997; Felton and Gentilet, 1997). Of course, **usually, detoxification reactions enable most of the AIA to be metabolised**, once again under the influence of the P450 cytochromes (see Wyss and Kaddurah-Daouk, 2000).

The nitrosation of creatine or creatinine, under the effect of nitrates reduced to nitrites, in the stomach, successively produces sarcosine, N-nitrososarcosine then N-nitrosodimethylamine. Creatine can also, like creatinine, form methylguanidine with successive transformation into methylnitrosocyanamide and methylnitrosourea. Methylnitrosocyanamide is probably the most mutagenic compound (Endo *et al.*, 1973, 1974). N-nitrosodimethylamine originating directly from creatine is also a highly toxic carcinogen formed in the small intestine, which has already been demonstrated in uraemic patients (Lele *et al.*, 1983).

Finally, Wyss and Kaddurah-Daouk (2000) estimate that **it is probable that these reactions exist but are very limited in the digestive tract of healthy Man.** It should be noted that the presence of iron seems to accentuate the carcinogenic risk while Vitamin C, through the inhibition of nitrosation, has a contrary effect, as do lactic bacteria, antioxidants, flavonoids, chlorophyll... (Ref. 20, 153, 235, 328, 363, 416 etc. in Wyss and Kaddurah-Daouk, 2000). When one knows the attacks to which the digestive tract is subject during exercise (ischaemia / reperfusion), again one must raise the issue of risk. We would point out that athletes are generally advised against ingesting creatine a short time before exercise (ineffective, it would seem) and taking iron supplements without medical advice.

Naturally, all these facts provide areas for discussion or exploration and raise issues. However, Rossi *et al.* (1998) unhesitatingly wrote: ***"The scientific data available on highly trained athletes indicates that this population does not benefit from creatine supplementation. The widespread use of creatine to improve competition performance does not seem to be justified and several questions regarding its use must be posed.***
In biological systems, creatine in excess undergoes condensation with sugar derivatives to form heterocyclic, carcinogenic amines. In a recent study supplementation of creatine tended to enhance the growth of Ehrlich ascite tumor cells.
The use of creatine goes against current doping regulations because the International Olympic Committee on doping legislation states that any physiological substance taken in abnormal quantities with the attention of artificially and unfairly increasing performance should be considered doping and violating the ethics of sport. In view of this rule, athletes should consider the legal and ethical position underlying the nutraceutical use of creatine.
The cancer risk related to abuse of this substance is too great to be taken lightly to have an unfair ridiculously low advantage of others in sorts competition. Athletes in this way pay too much for penny whistle.

7.7. Creatine supplementation and other mutagenic effects

A search on the *Medline*® database, *PubMed* of the *National Library of Medicine*, an international reference source, using the terms "creatine" and "toxicity...", brought up the articles already mentioned but also one by Yu and Deng (2000); they put forward the hypothesis of a ***"potential toxic effect of the chronic administration of creatine, a nutritional supplement to enhance sports performance".*** **Creatine is metabolised to methylamine, then converted into formaldehyde** with the role of semi-carbazide-sensitive amine oxydase in a cascade of reactions, requiring enzymes which are already present in the body. Why is this important? It would imply, in effect, the ingestion of creatine in large quantities over a long period and a reduction in renal excretion. The case advanced by the authors, for renal lesions caused by creatine making this risk possible, have until now, been largely invalidated (see Poortmans and Francaux): this line of argument, based on renal lesions to explain increased renal retention, could thus be seen as debatable. But the hypothesis is based on a reduction in renal excretion, to which the hypothetical lesions attempt to give substance. During daily training, whether for team sports, muscle building,

bodybuilding or others, several hours are spent on the field or in the gym, often causing considerable sweat production and therefore dehydration, as the exercise is repeated and of high intensity and the environment is often hot (gyms). And most sportsmen do not rehydrate sufficiently. This is a known fact. One may deplore it, write about correcting it, but this is the reality on the ground, and it is undeniable. And episodes of splanchnic ischaemia have been described in the digestive tract and the kidneys, with a considerable reduction in blood flow (Qspl). A figure of 80% has been put forward, which means that Qspl is then 1/5 of that at rest, resulting in a considerable reduction in renal excretion, only very partially compensated by sweat excretion. These are the conditions described by the authors in sportsmen taking quantities of creatine often far higher than what is theoretically recommended (10 g/d and more instead of 2-4 g/d, a small amount, close to the intake and physiological synthesis which they are merely replacing and it is certainly the case that other recommendations are followed for far higher doses), while the alteration in their renal function is admittedly reversible, renal excretion is reduced, for which sweating only partially compensates.

Formaldehyde is a toxic aldehyde; it is known as a "cross-linker" for protein and DNA molecules, which are broken down or unable to replicate and lose their functions, as the physiological repair mechanisms are incomplete (Quievryn and Zhitkovich, 2000). It is implicated in vascular pathologies, nephropathies, diabetes complications (Yu and Deng, 2000) and the onset of neurological disorders; **it is above all responsible for genotoxicity (Headlam *et al.*, 2000) and carcinogenic effects** on the digestive tract (Blasiak *et al.*, 2000). And this carcinogenicity is acknowledged by the authorities. The International Agency for Research on Cancer (IARC), part of the World Health Organisation (WHO), has a website (and a unit researching nutrition and cancer: Director: Dr Riboli), www.iarc.fr. In one of its sections, over 800 products studied are listed according to their degree of carcinogenic effect. They are categorised as 1, carcinogenic, 2A, potentially and 2B possibly carcinogenic, 3, effects not fully known, and 4 probably not carcinogenic. While creatine has not been studied (there are thousands of eligible chemical substances), **formaldehyde appears in the IARC international classification system as a 2A substance**...

This is clear and serious enough for studies to be conducted to verify whether or not in the actual situation on the ground, these substances are produced in the sportsman.

In conclusion, chronic ingestion of creatine could be the source of major toxicological risks to health, especially in the very long term. These are based mainly on hypotheses, but in view of their extreme gravity and even if adverse incidents may take several decades to appear, scientific proof of the existence or absence of this risk must be provided. And in this instance, as far as the public authorities are concerned, this proof should be provided by the petitioners, the beneficiaries of any future licence for sale, meaning the producers and/or distributors of creatine.

8. Position of the American College of Sports Medicine.

The American College of Sports Medicine Roundtable on the physiological and health effects of oral creatine supplementation. Med. Sci. Sports Exerc, Vol. 32, No.3, pp.706-717, 2000.

"*Creatine (Cr) supplementation has become a common practice among professional, elite, collegiate, amateur, and recreational athletes with the expectation of enhancing exercise performance. Research indicates that Cr supplementation can increase muscle phosphocreatine (PCr) content, but not in all individuals. A high dose of 20 g.d -1 that is common to many research studies is not necessary, as 3g.d -1 will achieve the same increase in PCr given time. Coincident ingestion of carbohydrate with Cr may increase muscle uptake; however, the procedure requires a large amount of carbohydrate. Exercise performance involving short periods of extremely powerful activity can be enhanced, especially during repeated bouts of activity. This is in keeping with the theoritical importance of an elevated PCr content in skeletal muscle. Cr supplementation does not increase ma ximal isometric strength, the rate of maximal force production, nor œrobic exercise performance. Most of the evidence has been obtained from healthy young adult male subjects with*

mixed athletic ability and training status. Less research information is available related to the alterations due to age and gender. Cr supplementation leads to weight gain within the first few days, likely due to water retention related to Cr uptake in the muscle.Cr supplementation is associated with an enhanced accrual of strength in strenght –training programs, a response not independant from the initial weight gain, but may be related to a greater volume and intensity of training that can be achieved. There is no definitive evidence that Cr supplementation causes gastrointestinal, renal, and/or muscle cramping complications. The potential acute effects of high-dose Cr supplementation on body fluid balance has not been fully investigated and ingestion of Cr before or during exercise is not recommended. There is evidence that medical use of Cr supplementation is warranted in certain patients (e.g., neuromuscular disease); future research may establish its potential usefulness in other medical applications. Although Cr supplementation exhibits small but significant physiological and performance changes, the increases in performance are realized during very specific exercise conditions. This suggests that the apparent high expectations for performance enhancement, evident by the extensive use of Cr supplementation, are inordinate."

In view of such divergent views on the health effects: some claims state that no significant harmful effect has been proven and that one can safely try the ingestion of creatine even at high dosage for a significant period; while others, on the other hand, proclaim major hazards to health in the medium or long term; on what principles should one work?

9. Creatine supplementation and the principle of precaution

Clearly, the harmful effects and therefore the potential risks of creatine, in particular those resulting from its ingestion in large quantities, as a loading dose, or chronically by some sportsmen, whether in the short, medium or especially the long term, are poorly defined, even though sport is supposed to be beneficial to the health of presumably healthy sportsmen and women.

We feel, therefore, that the principle of precaution fully applies to a product with proven positive effects on some performances, but not all, and with claims far surpassing what has been demonstrated scientifically, with no proven beneficial effect for the health of a previously and apparently healthy subject, but with possible side effects which are yet to be fully determined.

We should recall that the principle of precaution was envisaged in France, as part of a mission assigned by the Prime Minister to Professors Kourilsky and Vinet (1999, 2000).

It was also dealt with at European level, in the Treaty, in which Article 174 refers to it, in the section devoted to the environment. However, it is clearly stated that its area of application is much wider than the domain of the environment. *"it covers the special circumstances in which scientific data is insufficient, inconclusive or unreliable, but in which, based on indications arising from an objective and preliminary scientific assessment, there are reasonable causes for concern that the potentially dangerous effects on the environment and human, animal or plant health may be incompatible with the chosen level of protection."*

As this involves the health of sportsmen and women, a healthy population carrying out a physical or sporting activity with the aim of improving this health even more and with a connotation of well-being and longevity, we consider that the chosen level of protection should be especially high and that the public authorities should play a role of major responsibility in this choice.

"Recourse to the principle of precaution presupposes that the potentially dangerous effects of a phenomenon, product or process have been identified and that scientific assessment has not enabled the risk to be determined with sufficient certainty."
"The implementation of an approach based on the principle of precaution must start with a scientific assessment which is as comprehensive as possible and if possible, determining at each stage the level of scientific uncertainty."
"Examination, in the light of new scientific data, means that the measures based on the principle of precaution must be maintained as long as the scientific information is incomplete or inconclusive and the risk is still deemed to be too high for society to be subjected to it, in view of the appropriate level of protection. The measures must be regularly re-examined, in the light of scientific advances,

and modified where necessary."
"Attribution of the responsibility to provide scientific proof is already a frequent consequence of these measures. Countries which impose prior licensing (licensing for sale) on products with an a priori dangerous reputation, reverse the burden of proof by treating them as dangerous products unless and until the companies carry out the scientific research required to prove that they are not."
"When there is no prior licensing procedure, it may be up to the user or the public authorities to demonstrate the nature of a hazard and the level of risk of a product or process. In such cases, a specific precautionary measure may be taken to place the burden of proof on the producer, manufacturer or importer, but this cannot become a general rule."
(Communication from the European Commission, on recourse to the principle of precaution, 2000).
The Council of the European Union also adopted, on 13 April 1999, a resolution asking the Commission, among other things, *"to allow itself, in the future, to be guided even more by the principle of precaution, during the preparation of draft legislation and within the context of its other activities associated with consumer policy and to produce, as a priority, clear and effective guidelines with a view to the application of this principle."*
Similarly, the book entitled "The Principle of Precaution" (Kourilsy and Vinet, 2000), contains the sentence *"The absence of certainty should not delay the adoption of effective and proportionate measures to prevent serious and irreversible damage. "...*

Consequently, application of this principle of precaution to creatine supplements, whilst awaiting more in-depth studies, would result in its prescription and sale not being authorised and therefore its banning in the future, with this refusal being justified by appropriate information issued to users.

10. Creatine supplementation and sports regulations

There is no significantly increased physiological requirement for creatine in the sportsman and no dietary nutritional intake has been defined, the diet and endogenous synthesis enabling requirements to be met without any deficiency or pre-deficiency having been observed in the sportsman or more generally in healthy subjects.

Any exogenous intake of creatine is therefore based on supplementation, in excess of physiological requirements. At the present time, no upper safety limit has been defined for this product. Furthermore, research into health indicators appears incomplete; no insufficiency of creatine intake has been reported nor have any harmful effects been proven, only the potential for them, but this does not presuppose that none exists.

Sweat loss of creatine or creatinine, unlike that of urea, has not been precisely assessed and even if there were increased loss, diet and especially endogenous synthesis are capable of adapting to satisfy needs.

The concept of sport (see regulations on guidance in sport, AFSVFP, Ethics and illegal drug use, 1999) is mainly based on performance obtained solely by training, to each person's ability, in compliance with the regulations, spirit and ethics of sport, of fair play and non-violence, of exemplarity and ideal. It is true that these are often called into question by repeated acts of cheating and punished to a greater or lesser extent, but the public authorities, like the sports authorities, have decided to control them through laws, decrees and orders.

The alternative to drug-taking lies in a balanced and varied diet, adjusted to the specific needs of the sportsman in accordance with the rules set out in the CEDAP decrees and opinions and the RDAs, and not in supplements. The search, demand for and use of miracle products through supplements is, in fact, a first step in the seeking of performance or sensation by means other than natural ones. This is therefore a cheat's approach, the self-styled search for a compromise which is in fact based on false representations with an erroneous value system, contributing to the dream that performance can be achieved by external means, not actually recognised by the institutions. This damages the value system, the indicators and the integrity of the sporting ethic, insidiously creating confusion in the sportsman's mind, his judgement too often weakened by the pressures and challenges he is facing. He is often defenceless when this is suggested to him, and there is always someone in his circle prepared to do so, with products which are increasingly effective, ultimately

illicit and therefore prohibited. (Depiesse and Pérès, 1999).

Creatine contributes to this dream with its tempting claims, the majority of which, it transpires, are unjustified.

The sportsman, through his training and performance programme, exposes himself to a risk which, by means of the rules of sport, is in principle calculated to be a limited one. But in fact, the risk of morbidity and mortality in sport is currently considered to be high, with over one thousand deaths annually on sports fields and several million accidents. The risk is therefore proven and requires preventive measures. It seems questionable to add to this a risk from chemicals, alongside the physical risks. The recourse to the principle of precaution again seems justified here.

The attention of the relevant public authorities, the French Ministry for Sport and Youth and its Departments, the representative Federations and the sports authorities representing the Olympic Committee in France should be drawn to the potential risks, on the one hand to health and on the other hand, to sports regulations and ethics, of the ingestion of creatine in the form of a supplement, the conditions of which provide an encouragement to bend the rules, leading to illegal drug taking.

11. Conclusion and proposed opinion

These are given in the Opinion issued by the Agence Française de Sécurité Sanitaire des Aliments (AFSSA); please refer to them.

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Annexes

Annexes to the report submitted to AFSSA:

- Report of the Scientific Committee on Food on composition and specification of food intended to meet the expenditure of intense muscular effort, especially for sportsmen, pp 36-38, 11 july 2000

- Opinion of the Scientific Committee on Food on safety aspects of creatine supplementation, pp6, 12/9/2000

- The SN/AEMS Web Report Search Results for *creatine* (FDA, CFSAN, OSN)

- Title and abstract: The physiological and health effects of oral creatine supplementation (American College of Sports Medicine). Med Sci Sports Exerc, 2000, 32, 706-717.